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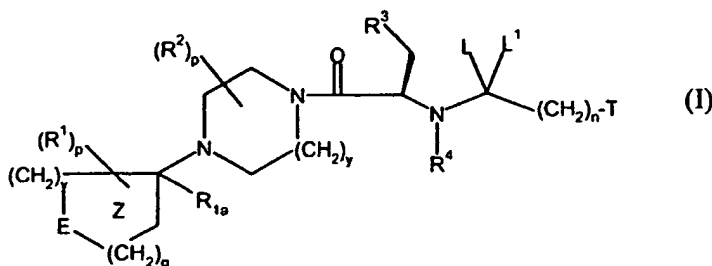
Declarations under Rule 4.17:

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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,

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WO 03/061660 A1

(54) Title: MELANOCORTIN RECEPTOR AGONISTS



(57) Abstract: The present invention relates to melanocortin receptor agonist of the formula (I): which is useful in the treatment for obesity, diabetes, and male and/or female sexual dysfunction.



BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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MELANOCORTIN RECEPTOR AGONISTS

FIELD OF THE INVENTION

5 The present invention relates to melanocortin receptor agonists, and as such are useful in the treatment of disorders responsive to the activation of melanocortin receptors, such as obesity, diabetes, and male and/or female sexual dysfunction.

BACKGROUND OF THE INVENTION

10 Pro-opiomelanocortin (POMC) derived peptides are known to affect food intake. Several lines of evidence support the notion that the G-protein coupled receptors (GPCRs) of the melanocortin receptor (MC-R) family, several of which are expressed in the brain, are targets of POMC derived peptides involved in the control of food intake and
15 metabolism.

 Evidence for the involvement of MC-R in obesity includes: i) the agouti (AVY) mouse which ectopically expresses an antagonist of the MC-1R, -3R and -4R is obese, indicating that blocking the action of these three MC-Rs can lead to hyperphagia and metabolic disorders; ii) MC-4R knockout mice (Huszar et al., *Cell*, 88:131-141, 1997)
20 recapitulate the phenotype of the agouti mouse and these mice are obese; iii) the cyclic heptapeptide MC-1R, -3R, -4R, and -5R agonist melanotanin-II (MT-II) injected intracerebroventricularly (ICV) in rodents, reduces food intake in several animal feeding models (NPY, *ob/ob*, agouti, fasted) while ICV injected SHU-9119 (MC-3R, -4R antagonist; MC-1R and -5R agonist) reverses this effect and can induce hyperphagia; iv)
25 chronic intraperitoneal treatment of Zucker fatty rats with an α -NDP-MSH derivative melanocytes. MC-2R is expressed in the adrenal gland and represents the ACTH receptor. MC-3R is expressed in the brain, gut and placenta and may be involved in the control of food intake and thermogenesis. MC-4R is uniquely expressed in the brain and its inactivation was shown to cause obesity. MC-5R is expressed in many tissues
30 including white fat, placenta and exocrine glands. A low level of expression is also observed in the brain. MC-5R knock out mice reveal reduced sebaceous gland lipid production (Chen et al., *Cell*, 91:789-798, 1997).

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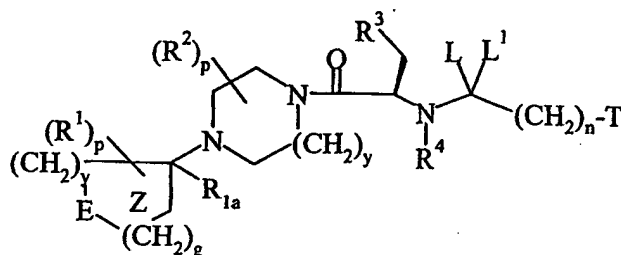
Evidence for the involvement of MC-R in male and/or female sexual dysfunction is detailed in WO 00/74670.

Melanocortin receptor agonist compounds were disclosed in WO 99/64002.

5

BRIEF SUMMARY OF THE INVENTION

The present invention relates to a compound of formula I:



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof,

10 wherein:

L and L^1 are both hydrogen or combine together to form an oxo group;

E is: O , S , NR^{1b} , SO , SO_2 , CR^9 , or $C(R^9)_2$, provided that when E is CR^9 , or $C(R^9)_2$, R^9 may combine with an adjacent R^1 to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

15 wherein the Z ring has 0, or 1 double bond;

R^1 is: hydrogen,

C_1 - C_8 alkyl,

C_2 - C_8 alkenyl,

C_2 - C_4 haloalkyl

20 (D) C_3 - C_7 cycloalkyl,

(D)phenyl,

aryl, or

$C(O)OC_1$ - C_8 alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted

25 with hydroxy, halo, C_1 - C_8 alkyl, C_1 - C_4 alkoxy, C_2 - C_4 haloalkyl, and (D) C_3 - C_7 cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

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R_{1a} is: hydrogen,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

5 (D)aryl,

(D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(CH₂)_mN(R⁸)₂,

10 (CH₂)_mNR⁸C(O)C₁-C₄ alkyl,

(CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),

(CH₂)_mOR⁸,

(CH₂)_mSC₁-C₄ alkyl,

(CH₂)_mSO(C₁-C₄ alkyl),

15 (CH₂)_mSO₂(C₁-C₄ alkyl), or

(CH₂)_mSO₂ N(R⁸)₂;

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally

substituted with one to five substituents independently selected from the group

consisting of perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy,

20 and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted
on a carbon atom adjacent to a heteroatom;

R^{1b} is: hydrogen,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

25 SO₂(C₁-C₈ alkyl),

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(D)CON(R⁸)₂, or

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SO₂(D)phenyl wherein the phenyl group is optionally substituted with one to five substituent selected from halo, and C₁-C₈ alkyl;

R² is: hydrogen,

C₁-C₈ alkyl,

5 CONHC₁-C₄ alkyl,

(D)phenyl, oxo, or

(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;

10 wherein phenyl, aryl and thienyl are optionally substituted with one to three substituents independently selected from the group consisting of:

cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl;

R⁴ is: hydrogen,

15 C₁-C₈ alkyl,

CH₂(CH₂)_mC₁-C₄ alkoxy,

C(O)C₁-C₄ alkyl or

C(O)OC₁-C₄ alkyl;

R is: hydroxy,

20 halo,

C₁-C₈ alkyl,

C₂-C₈ alkenyl,

C₁-C₈ alkoxy,

C₁-C₄ haloalkyl,

25 (D)C₃-C₇ cycloalkyl,

(D)aryl,

(D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

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(D)C(O)heteroaryl,
(D)N(R⁸)₂,
(D)NR⁸C(O)C₁-C₄ alkyl,
(D)NR⁸SO₂(C₁-C₄ alkyl),
5 (D)OC₁-C₄ alkyl,
(D)OC(O)C₁-C₄ alkyl,
(D)heterocyclic,
(D)SC₁-C₄ alkyl, or
(D)SO₂N(R⁸)₂;

10 wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic,
and heteroaryl are optionally substituted with one to five substituents
independently selected from R⁸; and provided that when R is halo or hydroxy it is
not substituted on a carbon adjacent to a heteroatom;

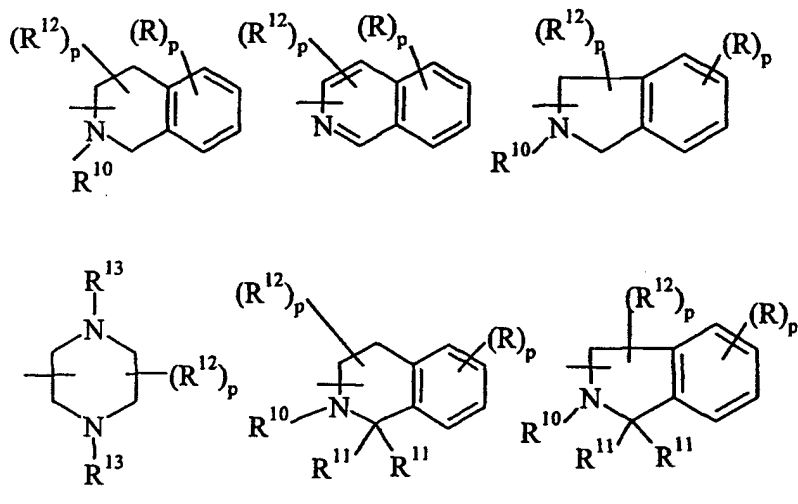
each R⁸ is independently:

15 hydrogen,
oxo,
C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
phenyl,
20 aryl or
heteroaryl,

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl,
aryl and heteroaryl are optionally substituted with one to three substituents
selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided
25 that the halo and hydroxy groups are not substituted on a carbon adjacent to a
heteroatom;

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T is:

 R^9 is independently:

- 5 hydrogen,
 (C_1-C_8) alkyl,
 C_2-C_8 alkenyl,
 $C(O)C_1-C_8$ alkyl,
 C_2-C_8 alkynyl,
 10 phenyl,
 aryl, or
 heteroaryl;

 R^{10} is: hydrogen,

- 15 (C_1-C_8) alkyl,
 C_3-C_8 alkenyl,
 $C(O)C_1-C_8$ alkyl,
 C_2-C_8 alkynyl,
 phenyl,
 20 aryl, or
 heteroaryl;

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R^{11} is independently:

hydrogen, (C₁-C₈) alkyl, or (D)phenyl, or aryl;

R^{12} is independently:

- 5 C₁-C₈ alkyl,
phenyl,
aryl,
heteroaryl,
(CH₂)_nN(R⁸)₂,
(CH₂)_nNR⁸C(O)C₁-C₄ alkyl,
10 (CH₂)_nNR⁸C(O)OC₁-C₄ alkyl,
(CH₂)_n(OCH₂CH₂)_qN(R⁸)₂,
(CH₂)_n(OCH₂CH₂)_qNR⁸C(O)C₁-C₄ alkyl,
(CH₂)_n(OCH₂CH₂)_qNR⁸SO₂(C₁-C₄ alkyl),
(CH₂)_n[O]_q(C₁-C₈)alkylheterocyclic; and wherein for R^{12} , n is 2-8 when R^{12} is
15 substituted on a carbon atom adjacent to a heteroatom;

R^{13} is independently:

- hydrogen,
C₁-C₈ alkyl,
20 (D)C₃-C₇ cycloalkyl,
(D)phenyl,
C(O)C₁-C₈ alkyl,
SO₂C₁-C₈ alkyl, or
SO₂-phenyl;
25 D is: a bond or C₁-C₄ alkyl;
g is: 0, 1, or 2;
y is: 1 or 2;
m is: 1-4;
n is: 0-8;

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p is: 0-4; and

q is: 0-1; and wherein,

aryl is defined as benzylic;

heteroaryl is defined as a monocyclic or bicyclic aromatic ring of 5 to 10 carbon
 5 atoms containing from one to three heteroatoms selected from O, N, or S; and
 heterocyclic is defined as a monocyclic, bicyclic, or tricyclic ring of 5 to 14 carbon atoms
 which can be aromatic or nonaromatic and containing from one to three heteroatoms
 selected from N, O, or S.

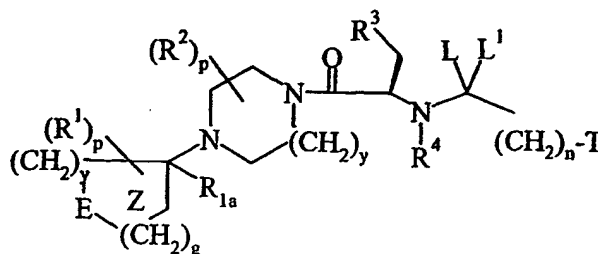
Another aspect of the present invention relates to a method for treating obesity or
 10 diabetes mellitus in a patient which comprises administering to said patient an effective
 amount of a compound of formula I, or a pharmaceutical salt, solvate, enantiomer or
 prodrug thereof, wherein said compound is an agonist of the melanocortin-4 receptor.

Another aspect of the present invention relates to a method for treating male or
 female sexual dysfunction, including erectile dysfunction, which comprises administering
 15 to said male or female an effective amount of a compound of formula I, or a
 pharmaceutical salt thereof, wherein said compound is an agonist of the melanocortin-4
 receptor.

In addition, the present invention relates to a use of a compound of formula I in
 treating obesity or diabetes.

20 The present invention also relates to the use of a compound of formula I in
 treating male or female sexual dysfunction, including erectile dysfunction wherein said
 compound is an agonist of the melanocortin-4 receptor.

The present invention relates to the use of a compound of formula I:



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein

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wherein:

L and L¹ are both hydrogen or combine together to form an oxo group;

E is: O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹ may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

R¹ is selected from the group consisting of:

hydrogen,

C₁-C₈ alkyl,

10 C₂-C₈ alkenyl,

C₂-C₄ haloalkyl

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

15 C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇ cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom.

20 R_{1a} is: hydrogen,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

(D)aryl,

25 (D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(CH₂)_mN(R⁸)₂,

(CH₂)_mNR⁸C(O)C₁-C₄ alkyl,

30 (CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),

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$(\text{CH}_2)_m\text{OR}^8$,
 $(\text{CH}_2)_m\text{SC}_1\text{-C}_4$ alkyl,
 $(\text{CH}_2)_m\text{SO}(\text{C}_1\text{-C}_4$ alkyl),
 $(\text{CH}_2)_m\text{SO}_2(\text{C}_1\text{-C}_4$ alkyl), or

5 $(\text{CH}_2)_m\text{SO}_2\text{N}(\text{R}^8)_2$;

wherein $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoro $\text{C}_1\text{-C}_4$ alkoxy, halo, hydroxy, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, and $\text{C}_1\text{-C}_4$ haloalkyl; provided that halo and hydroxy groups are not substituted
10 on a carbon atom adjacent to a heteroatom;

R^{1b} is: hydrogen,

$\text{C}_1\text{-C}_8$ alkyl,
 $(\text{D})\text{C}_3\text{-C}_7$ cycloalkyl,
 $\text{SO}_2(\text{C}_1\text{-C}_8$ alkyl),

15 $(\text{D})\text{C}(\text{O})\text{C}_1\text{-C}_4$ alkyl,
 $(\text{D})\text{C}(\text{O})\text{OC}_1\text{-C}_4$ alkyl,
 $(\text{D})\text{CON}(\text{R}^8)_2$, or

$\text{SO}_2(\text{D})\text{phenyl}$, wherein the phenyl group is optionally substituted with one to five substituent selected from halo, and $\text{C}_1\text{-C}_8$ alkyl;

20 R^2 is: hydrogen,

$\text{C}_1\text{-C}_8$ alkyl,
 $\text{CONHC}_1\text{-C}_4$ alkyl,
 $(\text{D})\text{phenyl}$,

oxo, or

25 $(\text{D})\text{C}_3\text{-C}_7$ cycloalkyl,

provided that when R^2 is oxo, R^2 is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R^3 is: phenyl, aryl or thienyl;

wherein phenyl, aryl and thienyl are optionally substituted with one to three substituents independently selected from the group consisting of:
cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl;

- 5 R⁴ is: hydrogen,
 C₁-C₈ alkyl,
 CH₂(CH₂)_mC₁-C₄ alkoxy,
 C(O)C₁-C₄ alkyl, or
 C(O)OC₁-C₄ alkyl;
- 10 R is: hydroxy,
 halo,
 C₁-C₈ alkyl,
 C₂-C₈ alkenyl,
 C₁-C₈ alkoxy,
- 15 C₁-C₄ haloalkyl,
 (D)C₃-C₇ cycloalkyl,
 (D)aryl,
 (D)heteroaryl;
- 20 (D)C(O)C₁-C₄ alkyl,
 (D)C(O)OC₁-C₄ alkyl,
 (D)C(O)heteroaryl,
 (D)N(R⁸)₂,
 (D)NR⁸C(O)C₁-C₄ alkyl,
 (D)NR⁸SO₂(C₁-C₄ alkyl),
- 25 (D)OC₁-C₄ alkyl,
 (D)OC(O)C₁-C₄ alkyl,
 (D)heterocyclic,
 (D)SC₁-C₄ alkyl, or

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(D)SO₂N(R⁸)₂;

wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic,
and heteroaryl are optionally substituted with one to five substituents
independently selected from R⁸; and provided that when R is halo or hydroxy it is
not substituted on a carbon adjacent to a heteroatom;

5

each R⁸ is independently:

hydrogen,

oxo,

10

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

phenyl,

aryl or

heteroaryl,

15

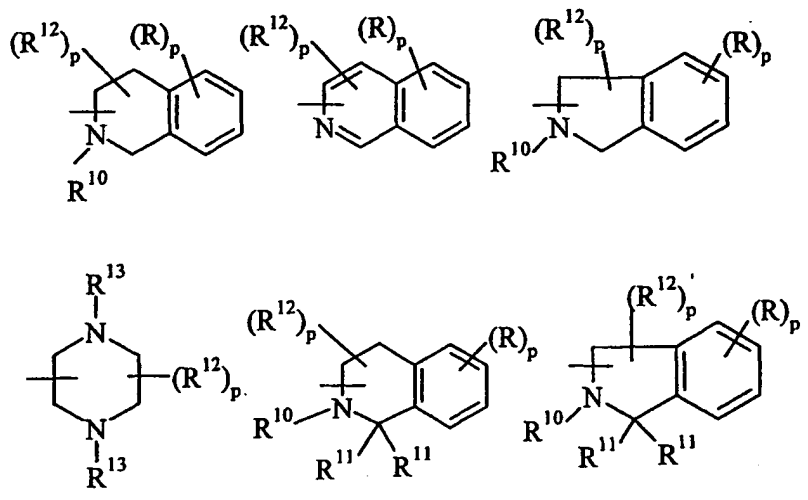
wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl,

aryl and heteroaryl are optionally substituted with one to three substituents
selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided
that the halo and hydroxy groups are not substituted on a carbon adjacent to a
heteroatom;

20

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T is:

 R^9 is independently:

- 5 hydrogen,
 (C_1-C_8) alkyl,
 C_2-C_8 alkenyl,
 $C(O)C_1-C_8$ alkyl,
 C_2-C_8 alkynyl,
 10 phenyl,
 aryl, or
 heteroaryl;

 R^{10} is; hydrogen,

- (C_1-C_8) alkyl,
 15 C_3-C_8 alkenyl,
 $C(O)C_1-C_8$ alkyl,
 C_2-C_8 alkynyl,
 phenyl,
 aryl, or
 20 heteroaryl;

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R^{11} is independently:

hydrogen, (C₁-C₈) alkyl, or (D)phenyl, or aryl;

R^{12} is independently:

- 5 C₁-C₈ alkyl,
 phenyl,
 aryl,
 heteroaryl,
 (CH₂)_nN(R⁸)₂,
 10 (CH₂)_nNR⁸C(O)C₁-C₄ alkyl,
 (CH₂)_nNR⁸C(O)OC₁-C₄ alkyl,
 (CH₂)_n(OCH₂CH₂)_qN(R⁸)₂,
 (CH₂)_n(OCH₂CH₂)_qNR⁸C(O)C₁-C₄ alkyl,
 (CH₂)_n(OCH₂CH₂)_qNR⁸SO₂(C₁-C₄ alkyl), or
 15 (CH₂)_n[O]_q(C₁-C₈)alkylheterocyclic; and wherein for R^{12} , n is 2-8 when R^{12} is
 substituted on a carbon atom adjacent to a heteroatom;

R^{13} is independently:

- hydrogen,
 20 C₁-C₈ alkyl,
 (D)C₃-C₇ cycloalkyl,
 (D)phenyl,
 C(O) C₁-C₈ alkyl,
 SO₂C₁-C₈ alkyl, or
 25 SO₂-phenyl;
 D is: a bond or C₁-C₄ alkyl;
 g is: 0, 1, or 2;
 y is: 1 or 2;
 m is: 1-4;

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n is: 0-8;

p is: 0-4; and

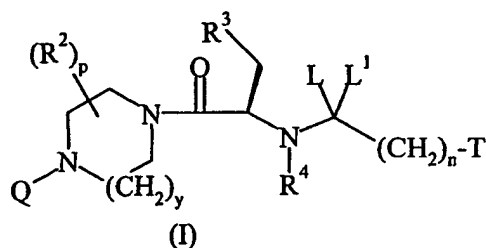
q is: 0-1; in the manufacture of a medicament for treating obesity and/or diabetes.

In addition, the present invention relates to a compound of formula I for use in
 5 treating obesity and/or diabetes in companion animals i.e. dogs, cats and the like wherein
 said compound is an agonist of the melanocortin-4 receptor.

Yet another aspect of the present invention relates to a pharmaceutical
 composition comprising a compound of formula I or a pharmaceutically acceptable salt
 thereof, and a pharmaceutical carrier.

10

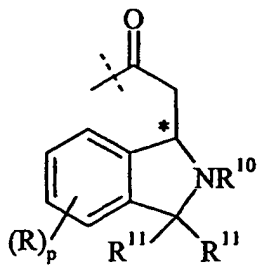
The present invention also provides a process for preparing a compound of
 formula I:



or a pharmaceutically acceptable salt or stereoisomer thereof,

15 wherein:

-CLL'-(CH₂)ₙ-T is:

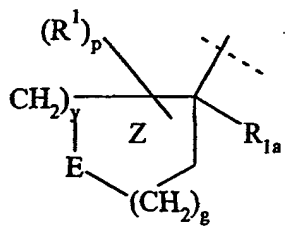


wherein R¹⁰ is a CBz or Boc protecting group, hydrogen, (C₁-C₈) alkyl, C₃-C₈ alkenyl,
 C(O)C₁-C₈ alkyl, C₂-C₈ alkynyl, phenyl, aryl, or heteroaryl;

20

-16-

Q represents the moiety:



wherein L and L¹ are both hydrogen or combine together to form an oxo group;

E is: O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹ may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

R¹ is selected from the group consisting of:

10 hydrogen,
C₁-C₈ alkyl,
C₂-C₈ alkenyl,
C₂-C₄ haloalkyl
(D)C₃-C₇ cycloalkyl,

15 (D)phenyl,
aryl,
C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇ cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom.

20 R_{1a} is: hydrogen,
C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
25 (D)phenyl,
(D)aryl,
(D)heteroaryl;

-17-

- (D)C(O)C₁-C₄ alkyl,
 (D)C(O)OC₁-C₄ alkyl,
 (CH₂)_mN(R⁸)₂,
 (CH₂)_mNR⁸C(O)C₁-C₄ alkyl,
 5 (CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),
 (CH₂)_mOR⁸,
 (CH₂)_mSC₁-C₄ alkyl,
 (CH₂)_mSO(C₁-C₄ alkyl),
 (CH₂)_mSO₂(C₁-C₄ alkyl), or
 10 (CH₂)_mSO₂ N(R⁸)₂;
 wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom
 15 adjacent to a heteroatom;
 R^{1b} is: hydrogen,
 C₁-C₈ alkyl,
 (D)C₃-C₇ cycloalkyl,
 SO₂(C₁-C₈ alkyl),
 20 (D)C(O)C₁-C₄ alkyl,
 (D)C(O)OC₁-C₄ alkyl,
 (D)CON(R⁸)₂, or
 SO₂(D)phenyl wherein the phenyl group is optionally substituted with one to five substituent selected from halo, and C₁-C₈ alkyl;
 25 R² is: hydrogen,
 C₁-C₈ alkyl,
 CONHC₁-C₄ alkyl,
 (D)phenyl,

-18-

oxo, or

(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;

5 wherein phenyl, aryl and thienyl are optionally substituted with one to three substituents independently selected from the group consisting of:
cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl;

R⁴ is: hydrogen,

10 C₁-C₈ alkyl,
CH₂(CH₂)_mC₁-C₄ alkoxy,
C(O)C₁-C₄ alkyl, or
C(O)OC₁-C₄ alkyl;

R is: hydroxy,

15 halo,
C₁-C₈ alkyl,
C₂-C₈ alkenyl,
C₁-C₈ alkoxy,
C₁-C₄ haloalkyl,
20 (D)C₃-C₇ cycloalkyl,
(D)aryl,
(D)heteroaryl;
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
25 (D)C(O)heteroaryl,
(D)N(R⁸)₂,
(D)NR⁸C(O)C₁-C₄ alkyl,
(D)NR⁸SO₂(C₁-C₄ alkyl),

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(D)OC₁-C₄ alkyl,
(D)OC(O)C₁-C₄ alkyl,
(D)heterocyclic,
(D)SC₁-C₄ alkyl, or

5

(D)SO₂N(R⁸)₂;

wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic,
and heteroaryl are optionally substituted with one to five substituents
independently selected from R⁸; and provided that when R is halo or hydroxy it is
not substituted on a carbon adjacent to a heteroatom;

10

each R⁸ is independently:

hydrogen,

oxo,

C₁-C₈ alkyl,

15

(D)C₃-C₇ cycloalkyl,

phenyl,

aryl or

heteroaryl,

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally

20

substituted with one to three substituents selected from the group consisting of
C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are
not substituted on a carbon adjacent to a heteroatom;

R⁹ is independently:

25

hydrogen,

(C₁-C₈) alkyl,

C₂-C₈ alkenyl,

C(O)C₁-C₈ alkyl,

C₂-C₈ alkynyl,

-20-

phenyl,
aryl, or
heteroaryl;

R^{11} is independently:

5 hydrogen, (C₁-C₈) alkyl, or (D)phenyl, or aryl;

D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

y is: 1 or 2;

m is: 1-4;

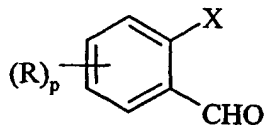
10 n is: 0-8;

p is: 0-4; and

q is: 0-1;

comprising the steps of:

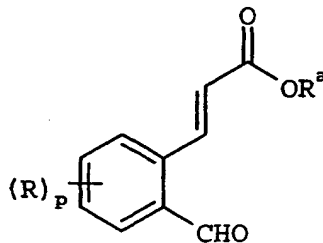
a) reacting a compound having a structural formula 1:



15

(1)

with $CH_2CH=C(O)OR^a$ wherein R^a is hydrogen or C₁-C₈ alkyl and X is halo, in the presence of a catalyst and a base in a suitable organic solvent to give the compound of formula 2:

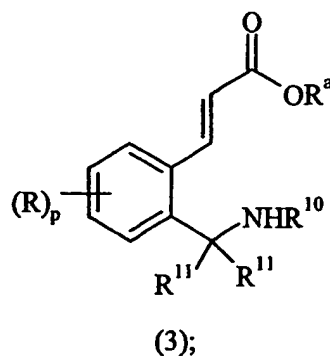


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(2);

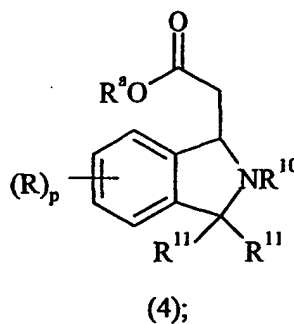
-21-

b) reductively aminating the compound of formula 2 in the presence of amine to give a compound of formula 3:



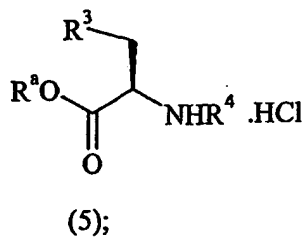
5

c) cyclizing the compound of formula 3 by Michael addition to give a compound of formula 4 or stereoisomers thereof:



10

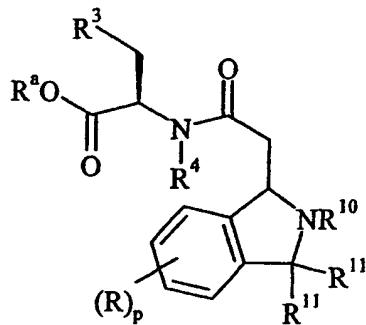
d) coupling the compound of formula 4 or stereoisomers thereof wherein R^a is H, with a compound of formula 5:



15

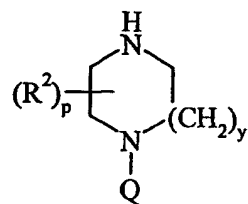
-22-

wherein R^a is C_1 - C_8 alkyl, to give a compound of formula 6:



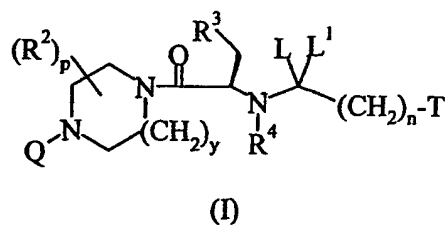
(6); and

- 5 e) coupling the compound of formula 6 wherein R^a is H, with a compound having a structural formula:



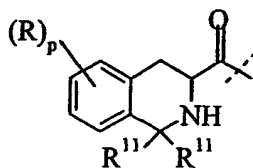
to afford the compound of formula 1.

- The present invention also provides a process for preparing a compound of
10 formula I:



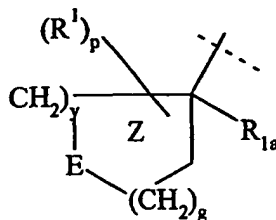
or a pharmaceutically acceptable salt or stereoisomer thereof,
wherein:

- 15 $-LL'(CH_2)_n-T$ is represented by the group:



-23-

Q represents the moiety:



E is: O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹ may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

R¹ is selected from the group consisting of:

hydrogen,

C₁-C₈ alkyl,

10 C₂-C₈ alkenyl,

C₂-C₄ haloalkyl

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

15 C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇ cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

20 R_{1a} is: hydrogen,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

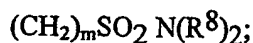
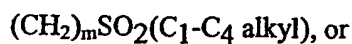
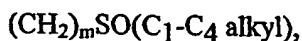
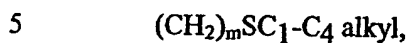
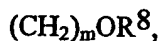
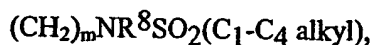
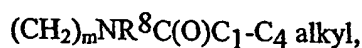
(D)aryl,

25 (D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

-24-



10 wherein $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoro $\text{C}_1\text{-C}_4$ alkoxy, halo, hydroxy, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, and $\text{C}_1\text{-C}_4$ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

R^{1b} is: hydrogen,

15 $\text{C}_1\text{-C}_8$ alkyl,

$(\text{D})\text{C}_3\text{-C}_7$ cycloalkyl,

$\text{SO}_2(\text{C}_1\text{-C}_8 \text{ alkyl}),$

$(\text{D})\text{C}(\text{O})\text{C}_1\text{-C}_4 \text{ alkyl},$

$(\text{D})\text{C}(\text{O})\text{OC}_1\text{-C}_4 \text{ alkyl},$

20 $(\text{D})\text{CON}(\text{R}^8)_2, \text{ or}$

$\text{SO}_2(\text{D})\text{phenyl}$ wherein the phenyl group is optionally substituted with one to 1 to 5 substituent selected from halo, and $\text{C}_1\text{-C}_8$ alkyl;

R^2 is: hydrogen,

$\text{C}_1\text{-C}_8$ alkyl,

25 $\text{CONHC}_1\text{-C}_4 \text{ alkyl},$

$(\text{D})\text{phenyl},$

oxo, or

-25-

(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;

wherein phenyl, aryl and thienyl are optionally substituted with one to three

5 substituents independently selected from the group consisting of:

cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl;

R⁴ is: hydrogen,

C₁-C₈ alkyl,

10 CH₂(CH₂)_mC₁-C₄ alkoxy,

C(O)C₁-C₄ alkyl or

C(O)OC₁-C₄ alkyl;

R is: hydroxy,

halo,

15 C₁-C₈ alkyl,

C₂-C₈ alkenyl,

C₁-C₈ alkoxy,

C₁-C₄ haloalkyl,

(D)C₃-C₇ cycloalkyl,

20 (D)aryl,

(D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(D)C(O)heteroaryl,

25 (D)N(R⁸)₂,

(D)NR⁸C(O)C₁-C₄ alkyl,

(D)NR⁸SO₂(C₁-C₄ alkyl),

(D)OC₁-C₄ alkyl,

-26-

(D)OC(O)C₁-C₄ alkyl,

(D)heterocyclic,

(D)SC₁-C₄ alkyl, or

(D)SO₂N(R⁸)₂;

5 wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic, and heteroaryl are optionally substituted with one to five substituents independently selected from R⁸, and provided that when R is halo or hydroxy it is not substituted on a carbon adjacent to a heteroatom;

10 each R⁸ is independently:

hydrogen,

oxo,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

15 phenyl,

aryl or

heteroaryl,

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to three substituents selected from the group consisting of

20 C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are not substituted on a carbon adjacent to a heteroatom;

R⁹ is independently:

hydrogen,

25 (C₁-C₈) alkyl,

C₂-C₈ alkenyl,

C(O)C₁-C₈ alkyl,

C₂-C₈ alkynyl,

phenyl,

30 aryl, or

-27-

heteroaryl;

 R^{10} is: hydrogen,(C₁-C₈) alkyl,C₃-C₈ alkenyl,5 C(O)C₁-C₈ alkyl,C₂-C₈ alkynyl,

phenyl,

aryl, or

heteroaryl;

10

 R^{11} is independently:hydrogen, (C₁-C₈) alkyl, or (D)phenyl, or aryl;D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

15 y is: 1 or 2;

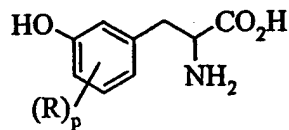
m is: 1-4;

n is: 0-8;

p is: 0-4; and

q is: 0-1;

20 comprising the steps of:

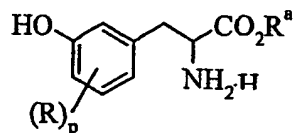
a) esterifying a compound of formula 1 with an alcohol R^aOH

(1)

25

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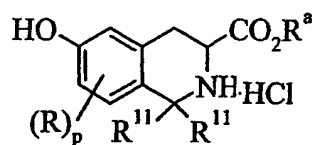
to form a compound of formula 2:



(2)

wherein R^a is a group selected from C_1 - C_4 alkyl, and (D) phenyl;

- 5 b) reacting a compound of formula 2 with $R^{11}COR^{11}$ to form a compound of formula:

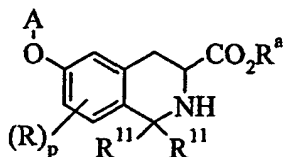


(3)

wherein R^{11} is independently hydrogen, C_1 - C_4 alkyl;

10

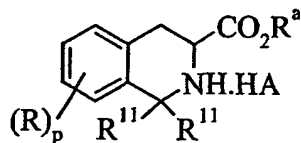
- c) reacting a compound of formula 3 with an activating group to form a compound of formula 4:



(4)

- 15 wherein A is an activating group;

- d) deoxygenating the compound of formula 4 by hydrogenation to afford a compound of formula 5:

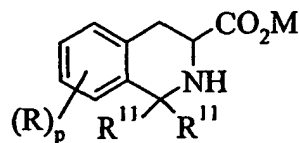


(5)

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-29-

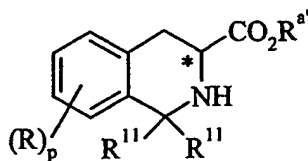
e) optionally reacting the compound of formula 5 wherein HA is an acidic, with an inorganic base to form a compound of formula 6:



(6)

5 wherein M is a univalent cation;

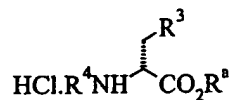
f) resolving the compound of formula 5 or the compound of formula 6 wherein M is hydrogen to afford a chiral compound of formula 7:



(7)

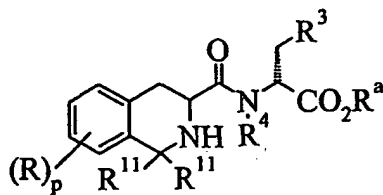
10 wherein Ra' is H or Ra;

g) coupling the compound of formula 7 with a compound of formula 8:



(8)

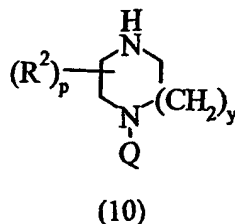
15 to afford a compound of formula 9:



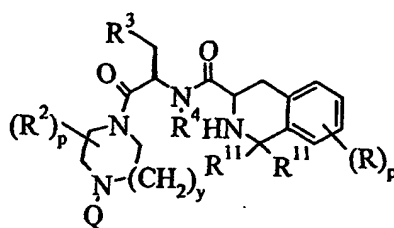
(9)

-30-

h) coupling the compound of formula 9 with a compound of formula 10:



to afford a compound of formula I:



I.

DETAILED DESCRIPTION OF THE INVENTION

Throughout the instant application, the following terms have the indicated meanings:

The term "C₁-C₈ alkyl" refers to a straight or branched saturated hydrocarbon moiety containing from 1 to 8 carbon atoms. The term "C₁-C₄ alkyl" refers specifically to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl. A "C₁-C₈ haloalkyl" is a C₁-C₈ alkyl moiety that is substituted with one or more halo atoms. One example of a haloalkyl group is trifluoromethyl. A "C₁-C₈ alkoxy" group is a C₁-C₈ alkyl group attached through an oxygen linker i.e. -OCH₃.

The term "benzofused bicyclic" as used herein refers to a bicyclic ring system or radical wherein one of the rings is the benzene ring and wherein the point of attachment to the backbone of the compound the invention is at other than the benzene ring. Unless otherwise specified it is to be understood that each ring of the benzofused bicyclic is optionally substituted with 1 to 3 substituents selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, cyano, alkoxy, alkoxyalkyl, amino, substituted amino, thiol, formyl, carboxy alkyl, carboxyester, carboxamide, and sulfonamido groups.

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The term "C₃-C₇ cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

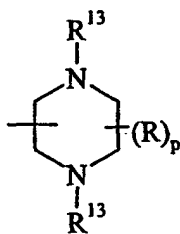
The term "hydrocarbon diradical" refers to a straight or branched chain of carbon atoms that may optionally be unsaturated at two or more carbons. Thus, a hydrocarbon
 5 diradical according to the present invention includes alkylene, alkenylene and alkylidene moieties. Examples include but are not intended to be limited to methylene, ethylene, propylene, butylene, -CH(CH₃)CH(CH₃)-, -CH₂C(CH₃)₂-, -CH₂CH(CH₃)CH₂-, -CH=CHCH₂-, -CH=CH-, -CH₂C≡CCH₂-, and the like.

The term "halo" refers to fluoro, chloro, bromo and iodo.

10 The term "perfluoroC₁-C₄ alkoxy" as used herein refers to C₁-C₄ alkoxy groups having from 1 to 5 fluorine atoms, and includes, for example, trifluoromethoxy and pentafluoroethoxy.

The term haloalkyl refers to a group having at least one carbon atom and as many halogen atoms as chemically sensible with or without hydrogen atoms, and positional
 15 isomers thereof. The term haloalkyl, therefore, includes but is not limited to groups such as trifluoromethyl, methylchloride, dichloromethyl, pentylchloride, butyl chloride, isopropyl chloride and the like.

As used herein a line "____" attached to a structure, partial structure of a molecule or fragment thereof, without a group attached at the end represents a point of attachment
 20 to another molecule, fragment or radical unless otherwise indicated. For example, the group:



shows the piperazine groups as being attachable to another molecule or fragment at any position of the piperazine ring where the valency allows i.e. the carbon atoms.

25 Unless otherwise specified, a "heterocycle" or "heterocyclic" or "heterocyclyl" group is a 5, 6 or 7 membered saturated, or partially unsaturated, or aromatic mono-cyclic

-32-

or benzofused bicyclic ring containing 1-5 heteroatoms selected from N, S or O, wherein said heterocycle is optionally substituted 1-4 times with:

C₁-C₈ alkyl, C₁-C₄ haloalkyl, (D)(C₃-C₇ cycloalkyl), unsubstituted-mono-cyclic nitrogen containing heterocycle, (D)NR⁸R⁸, (D)NR⁸C(O)C₁-C₈ alkyl, (D)NR⁸SO₂(C₁-C₈ alkyl), (D)SO(C₁-C₈ alkyl), (CH₂)_mSO₂R⁸, (CH₂)_mSO₂NR⁸R⁸ or (D)phenyl
5 wherein:

R⁸ is as described herein; or when two R⁸ groups are attached to the same nitrogen atom, said R⁸ groups, together with the nitrogen to which they are attached, may combine to form a nitrogen containing heterocycle.

10 The variable "D" at each occurrence is independently a bond or a C₁-C₄ hydrocarbon diradical.

Unless otherwise specified, a "nitrogen containing heterocycle" is a heterocycle that contains 1-4 nitrogen atoms and optionally contains 1 other heteroatom selected from O or S. Examples of nitrogen containing heterocycles includes but is not limited to 1,1-dioxo-1λ⁶-isothiazolidin-2-yl, pyrrole, thiazole, oxazolyl, imidazolyl, imidazolidinyl,
15 1,2,3-oxadiazolyl, piperidynyl, piperazinyl, pyrazinyl, pyrimidinyl, 1,3,5-triazinyl, morpholinyl, thiomorpholinyl, pyridazinyl, 1,3-4 thiadiazolyl, isothiazolyl, each optionally substituted with 1 to 3 substituents including for example halo, oxo, carboxy esters, carboxyamides, C₁-C₈ alkyl.

20 The term "oxo" as used herein refers to an oxygen atom formed by the combination of single bonds resulting in a double bond to oxygen. For example an "oxo" group formed by geminal substituents on a carbon atom depicts a carbonyl group i.e., an oxo group bonded to carbon.

The term "composition", as in pharmaceutical composition, is intended to
25 encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term "pharmaceutical" when used herein as an adjective means substantially
30 non-deleterious to the recipient patient.

The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other non-human animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

5 The terms "treating" and "treat", as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein.

 "Erectile dysfunction" is a disorder involving the failure of a male mammal to
10 achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, and inability to achieve an orgasm. An increase in erectile dysfunction is often associated with age and is generally caused by a physical disease or as a side effect of drug treatment.

15 "Female sexual dysfunction" encompasses, without limitation, conditions such as a lack of sexual desire and related arousal disorders, inhibited orgasm, lubrication difficulties, and vaginismus.

 Because certain compounds of the invention contain an acidic moiety (e.g., carboxy), the compound of formula I may exist as a pharmaceutical base addition salt
20 thereof. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like.

 Because certain compounds of the invention contain a basic moiety (e.g., amino),
25 the compound of formula I can also exist as a pharmaceutical acid addition salt. Such salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate,
30 maleate, 2-butyne-1,4-dioate, 3-hexyne-2,5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, beta-hydroxybutyrate,

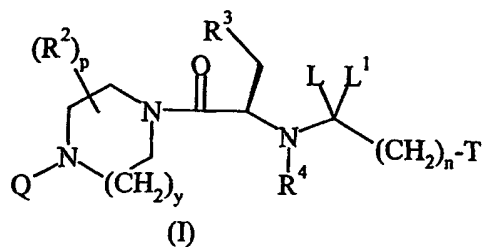
-34-

glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts. Preferred acid addition salts include the hydrochloride.

It will be understood that, as used herein, references to the compounds of formula I are meant to also include the pharmaceutical salts.

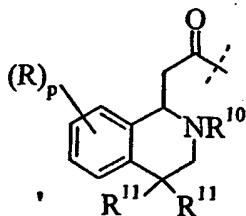
Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed within the scope of the present invention.

Another embodiment the present invention provides a process for preparing a compound of formula I:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

-LL'(CH₂)_n-T is represented by the group:

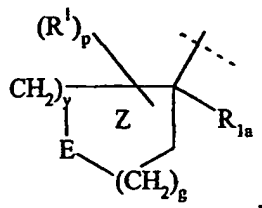


15

R¹⁰ is a CBz or Boc protecting group, hydrogen, (C₁-C₈) alkyl, C₃-C₈ alkenyl, C(O)C₁-C₈ alkyl, C₂-C₈ alkynyl, phenyl, aryl, or heteroaryl;

-35-

Q represents the moiety:



wherein E is O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹ may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

R¹ is: hydrogen,

C₁-C₈ alkyl,

C₂-C₈ alkenyl,

C₂-C₄ haloalkyl

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇ cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

R_{1a} is: hydrogen,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

(D)aryl,

(D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(CH₂)_mN(R⁸)₂,

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$(\text{CH}_2)_m \text{NR}^8 \text{C}(\text{O})\text{C}_1\text{-C}_4 \text{ alkyl},$

$(\text{CH}_2)_m \text{NR}^8 \text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl}),$

$(\text{CH}_2)_m \text{OR}^8,$

$(\text{CH}_2)_m \text{SC}_1\text{-C}_4 \text{ alkyl},$

5 $(\text{CH}_2)_m \text{SO}(\text{C}_1\text{-C}_4 \text{ alkyl}),$

$(\text{CH}_2)_m \text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl}), \text{ or}$

$(\text{CH}_2)_m \text{SO}_2 \text{N}(\text{R}^8)_2;$

wherein $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoro $\text{C}_1\text{-C}_4$ alkoxy, halo, hydroxy, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, and $\text{C}_1\text{-C}_4$ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

10 R^{1b} is: hydrogen,

$\text{C}_1\text{-C}_8$ alkyl,

15 $(\text{D})\text{C}_3\text{-C}_7$ cycloalkyl,

$\text{SO}_2(\text{C}_1\text{-C}_8 \text{ alkyl}),$

$(\text{D})\text{C}(\text{O})\text{C}_1\text{-C}_4 \text{ alkyl},$

$(\text{D})\text{C}(\text{O})\text{OC}_1\text{-C}_4 \text{ alkyl},$

$(\text{D})\text{CON}(\text{R}^8)_2, \text{ or}$

20 $\text{SO}_2(\text{D})\text{phenyl}$ wherein the phenyl group is optionally substituted with one to five substituent selected from halo, and $\text{C}_1\text{-C}_8$ alkyl;

R^2 is: hydrogen,

$\text{C}_1\text{-C}_8$ alkyl,

$\text{CONHC}_1\text{-C}_4 \text{ alkyl},$

25 $(\text{D})\text{phenyl},$

oxo, or

$(\text{D})\text{C}_3\text{-C}_7$ cycloalkyl, provided that when R^2 is oxo, R^2 is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

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R³ is: phenyl, aryl or thienyl;

wherein phenyl, aryl and thienyl are optionally substituted with one to three substituents independently selected from the group consisting of:

cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄

5 alkoxy, C₁-C₄ haloalkyl;

R⁴ is: hydrogen,

C₁-C₈ alkyl,

CH₂(CH₂)_mC₁-C₄ alkoxy,

C(O)C₁-C₄ alkyl, or

10 C(O)OC₁-C₄ alkyl;

R is: hydroxy,

halo,

C₁-C₈ alkyl,

C₂-C₈ alkenyl,

15 C₁-C₈ alkoxy,

C₁-C₄ haloalkyl,

(D)C₃-C₇ cycloalkyl,

(D)aryl,

(D)heteroaryl;

20 (D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(D)C(O)heteroaryl,

(D)N(R⁸)₂,

(D)NR⁸C(O)C₁-C₄ alkyl,

25 (D)NR⁸SO₂(C₁-C₄ alkyl),

(D)OC₁-C₄ alkyl,

(D)OC(O)C₁-C₄ alkyl,

(D)heterocyclic,

-38-

(D)SC₁-C₄ alkyl, or

(D)SO₂N(R⁸)₂;

wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic, and heteroaryl are optionally substituted with one to five substituents

5 independently selected from R⁸; and provided that when R is halo or hydroxy it is not substituted on a carbon adjacent to a heteroatom;

each R⁸ is independently:

hydrogen,

10 oxo,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

phenyl,

aryl or

15 heteroaryl,

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to three substituents selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are not substituted on a carbon adjacent to a heteroatom;

20

R⁹ is independently:

hydrogen,

(C₁-C₈) alkyl,

C₂-C₈ alkenyl,

25 C(O)C₁-C₈ alkyl,

C₂-C₈ alkynyl,

phenyl,

aryl, or

heteroaryl;

30

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R^{11} is independently:

hydrogen, (C₁-C₈) alkyl, or (D)phenyl, or aryl;

D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

5 y is: 1 or 2;

m is: 1-4;

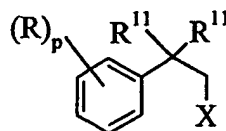
n is: 0-8;

p is: 0-4; and

q is: 0-1;

10 comprising the steps of:

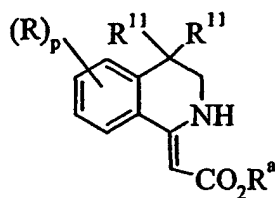
a) reacting a compound formula 1:



(1)

wherein X is halo and R^{11} is independently, hydrogen or C₁-C₄ alkyl, with CNCH₂CO₂R^a

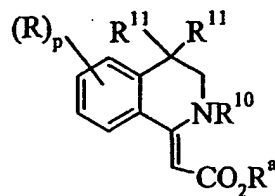
15 wherein R^a is C₁-C₈ alkyl, or benzyl to afford a compound of formula 2:



(2)

b) protecting the compound of formula 2 to form the compound of formula 3:

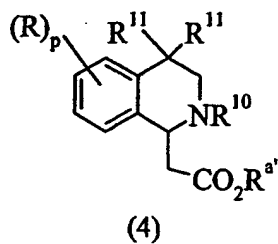
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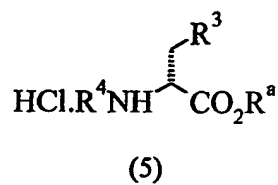
(3)

-40-

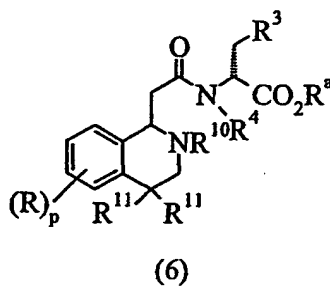
c) hydrogenating the compound of formula 3 to afford a compound of formula 4:



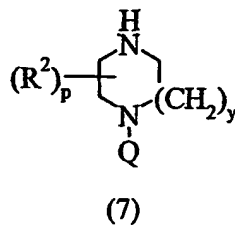
d) coupling the compound of formula 4 wherein R'a is hydrogen with a compound of formula 5:



to afford a compound of formula 6:

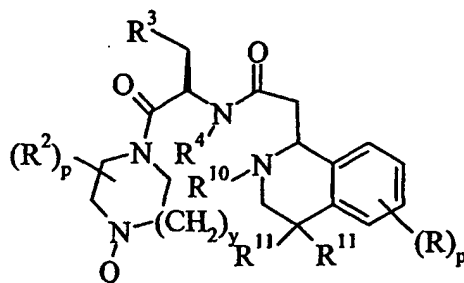


e) coupling the compound of formula 6 with a compound of formula 7:



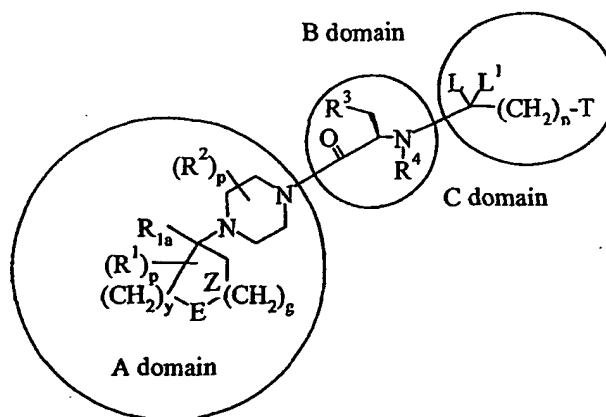
-41-

to afford a compound of formula I:



I.

- When describing various aspects of the present compounds, the terms “A domain” or “A” piece, “B domain” or “B” piece and “C domain” or “C” pieces are used below. This domain concept is illustrated below:



10 Utility

- Compounds of formula I are effective as melanocortin receptor agonists, particularly as agonists of the human MC-4 receptor. As melanocortin receptor agonists, the compounds of formula I are useful in the treatment of diseases, disorders or conditions responsive to the activation of one or more of the melanocortin receptors including, but not limited to, MC-1, MC-2, MC-3, MC-4, or MC-5. Diseases, disorders or conditions receptive to treatment with a MC-4 agonist include those mentioned *supra* and those described in WO 00/74679, the teachings of which are herein incorporated by reference.

Preferred Compounds of the Invention

The following listing sets out several groups of preferred compounds organized by domains. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

A Domains

A preferred compound of formula I is one having A-domain as listed below:

- 10 a) for the Z ring y is 1
- b) for the Z ring y is 2
- c) for the Z ring g is 1 or 2
- d) R_{1a} is:
- C₁-C₈ alkyl,
- 15 (D)C₃-C₇ cycloalkyl,
- (D)phenyl,
- (D)aryl,
- (D)heteroaryl,
- (CH₂)_mN(R⁸)₂,
- 20 (CH₂)_mNR⁸C(O)C₁-C₄ alkyl,
- (CH₂)_mNR⁸C(O)OC₁-C₄ alkyl,
- (CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),

wherein m is 1 or 2; and wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from halo, hydroxy and C₁-C₈ alkyl C₁-C₄ haloalkyl; wherein the halo, and hydroxy groups are not substituted on a carbon atom adjacent () to a heteroatom; and wherein for the group or subgroup -N(R⁸)₂, each R⁸ may combine with the other to form a nitrogen containing heterocycle;

- E is NR^{1b}, S, O, SO, SO₂ wherein R^{1b} is preferably hydrogen, C₁-C₈ alkyl,
- 30 (D)C(O)O C₁-C₄ alkyl, (D)CO C₁-C₄ alkyl, or (D)CON(R⁸)₂;
- E is O, NR^{1b}, SO₂, or S wherein R^{1b} is C₁-C₄ alkyl;

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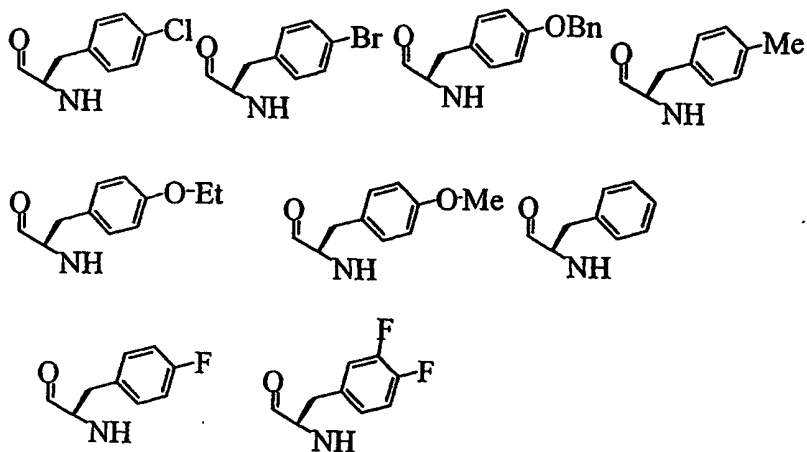
- e) When E is CR⁹ or C(R⁹)₂, one R⁹ group combines with an adjacent R¹ to form a benzene ring;
- f) The A-domain wherein the Z ring is completely saturated;
- g) The A domain wherein the R^{1a} is C₁-C₈ alkyl, C₂-C₈ alkenyl, (D)C₅-C₆ cycloalkyl, phenyl, or benzyl optionally substituted with halo;
- h) R¹ is selected from:
 - hydrogen,
 - Hydroxy,
 - Halo,
 - C₁-C₈ alkyl,
 - C₁-C₈ alkenyl,
 - C₁-C₄ haloalkyl,
 - (D)C₃-C₇ cycloalkyl,
 - (D)aryl,
 - (D)heteroaryl,
 - (D)C(O)C₁-C₈ alkyl,
 - (D)C(O)OC₁-C₈ alkyl,
 - (D)C(O)heteroaryl, or
 - (CH₂)_mN(R⁸)₂; provided that when R¹ is halo, or hydroxy, it is not substituted on a carbon atom adjacent () to a heteroatom; and p is 1.
- i) R² is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkoxy, (D)phenyl, or (D)C₃-C₇ cycloalkyl;

B Domains

- j) R³ is phenyl optionally para-substituted with halo, trifluoromethyl, benzyl, benzyloxy, C₁-C₂ alkyl or C₁-C₂ alkoxy;
- k) R³ is phenyl optionally ortho-substituted with halo, trifluoromethyl, benzyl, benzyloxy, C₁-C₂ alkyl or C₁-C₂ alkoxy;
- l) R³ is phenyl optionally ortho and para- disubstituted with halo, trifluoromethyl, benzyl, benzyloxy, C₁-C₂ alkyl or C₁-C₂ alkoxy;

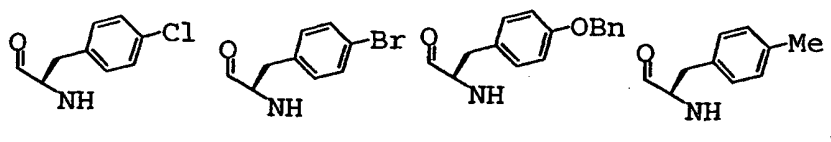
-44-

- m) R^3 is thienyl;
 n) R^3 is phenyl para-substituted with chloro;
 o) R^4 is selected from H, methyl, ethyl, COMe, and COOMe;
 p) the B domain is selected from the group consisting of:



5

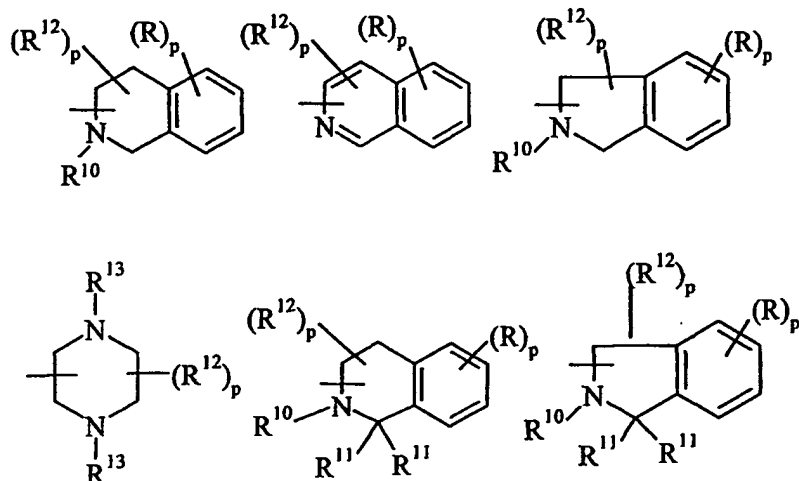
- q) the B domain is selected from the group consisting of:



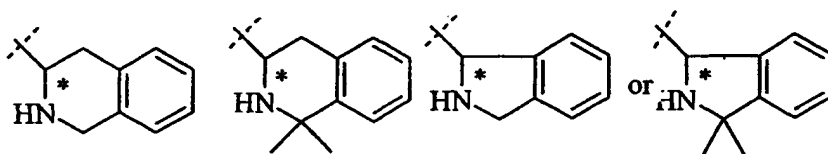
C Domains

The C-domain is represented by the formula $-CLL^1-T$. Preferred embodiments of the C-domain include:

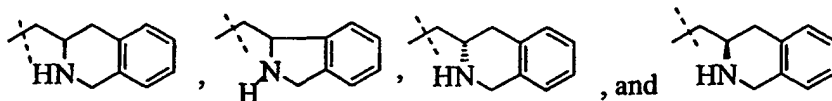
- 5 r) T of the C-domain is selected from the group consisting of:



- s) "T" of the C-domain is a moiety of the formula:

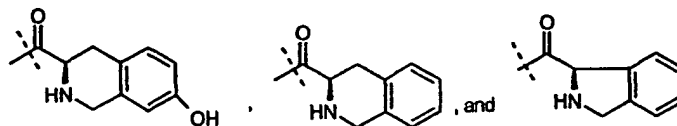


- t) "T" of the C domain is a moiety selected from the group consisting of:



10

- v) The C-domain is a moiety selected from the group consisting of:



- w) For $-LL^1(CH_2)_n-T$, n is 0, or 1 and LL^1 is oxo.

- x) For $-LL^1(CH_2)_n-T$, n is 0, or 1 and both L and L^1 are hydrogen.

15

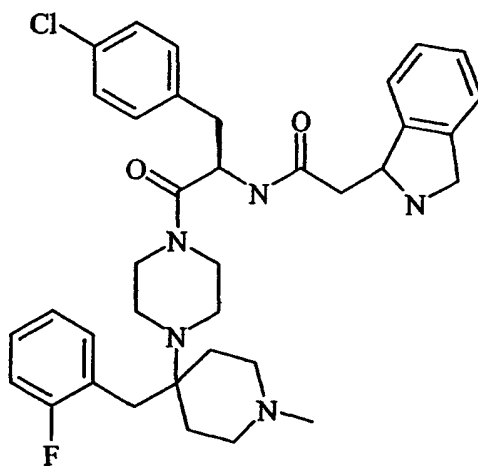
-46-

Salt Forms

- u) the compound of formula I is an acid addition salt;
- v) the compound of formula I is the hydrochloride salt.

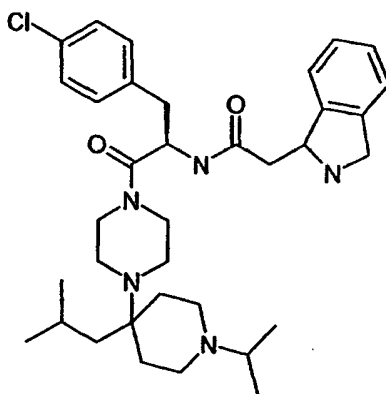
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Most preferred, is a compound selected from the group consisting of:



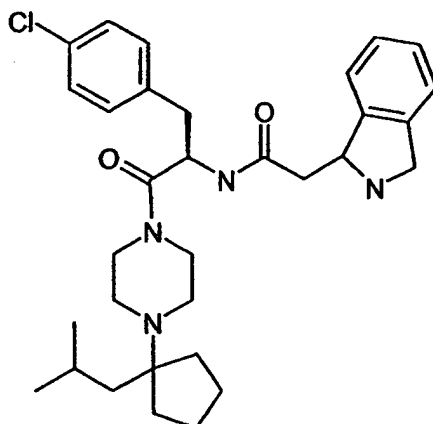
N-(1-(4-Chloro-benzyl)-2-{4-[4-(2-fluoro-benzyl)-1-methyl-piperidin-4-yl]-piperazin-1-yl}-2-oxo-ethyl)-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

10

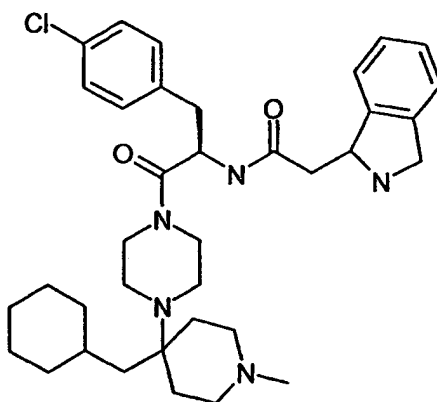


N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1-isopropyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-47-



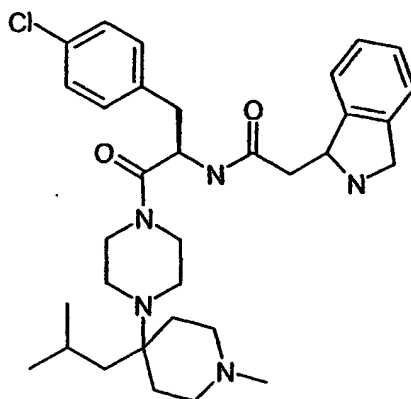
N-{1-(4-Chloro-benzyl)-2-[4-(1-isobutyl-cyclopentyl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



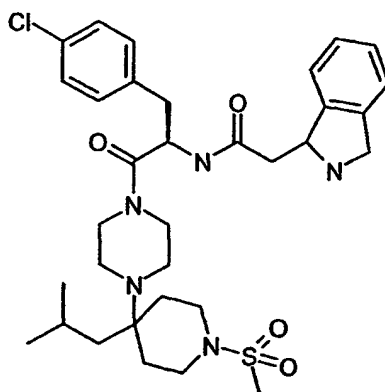
5

N-{1-(4-Chloro-benzyl)-2-[4-(4-cyclohexylmethyl-1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-48-



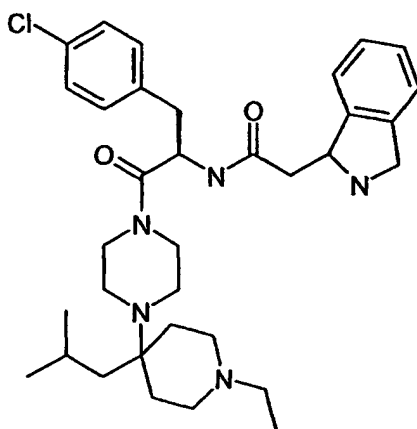
N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



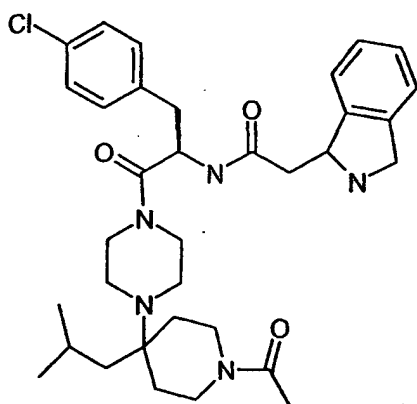
5

N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1-methanesulfonyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-49-



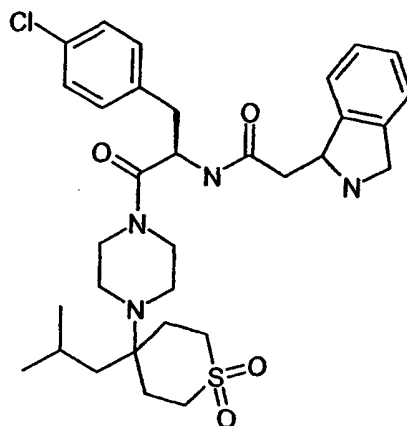
N-{1-(4-Chloro-benzyl)-2-[4-(1-ethyl-4-isobutyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



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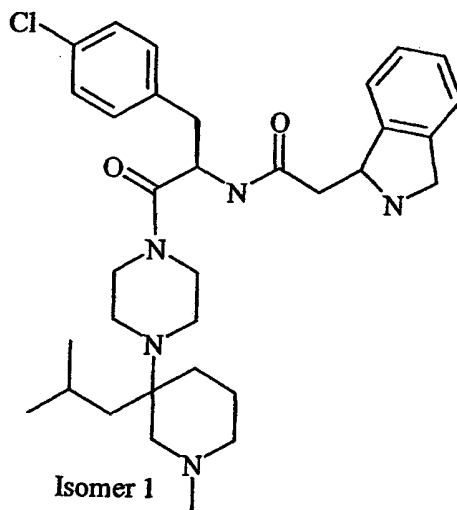
N-[2-[4-(1-Acetyl-4-isobutyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-chloro-benzyl)-2-oxo-ethyl]-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

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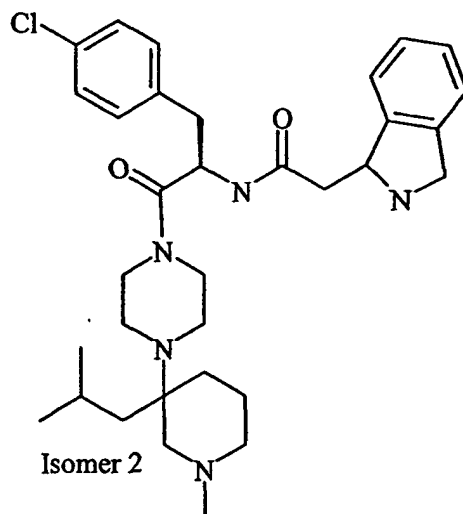
N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

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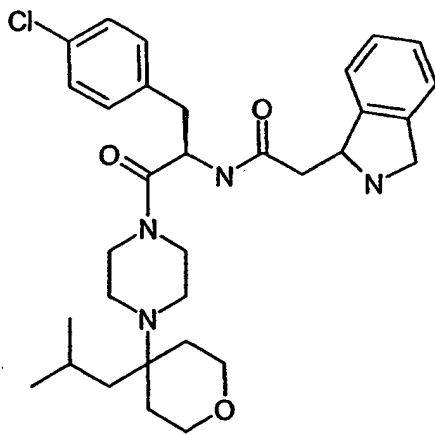
N-{1-(4-Chloro-benzyl)-2-[4-(3-isobutyl-1-methyl-piperidin-3-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

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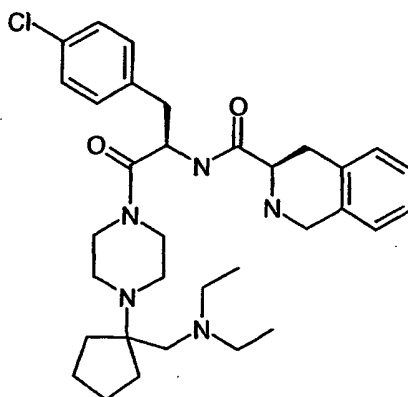
N-{1-(4-Chloro-benzyl)-2-[4-(3-isobutyl-1-methyl-piperidin-3-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

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N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-tetrahydro-pyran-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide, and

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1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chloro-benzyl)-2-[4-(1-diethylaminomethyl-cyclopentyl)-piperazin-1-yl]-2-oxo-ethyl}-amide, and its pharmaceutically acceptable salt, solvate, prodrug and enantiomer thereof.

5

Making Compounds of the Invention

The preparation of the compounds of the present invention may be carried out via sequential or convergent synthetic routes. The skilled artisan will recognize that the three domains of a compound of formula I are connected via amide bonds or NH-bonds. The skilled artisan can, therefore, readily envision numerous routes and methods of connecting the three domains via standard peptide coupling reaction conditions optionally followed by reduction to the amine as desired.

The phrase "standard peptide coupling reaction conditions" means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and HATU, in a inert solvent such as DCM, in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acids to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present can be found in Greene, et al., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC protecting groups are used extensively in the synthesis, and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive

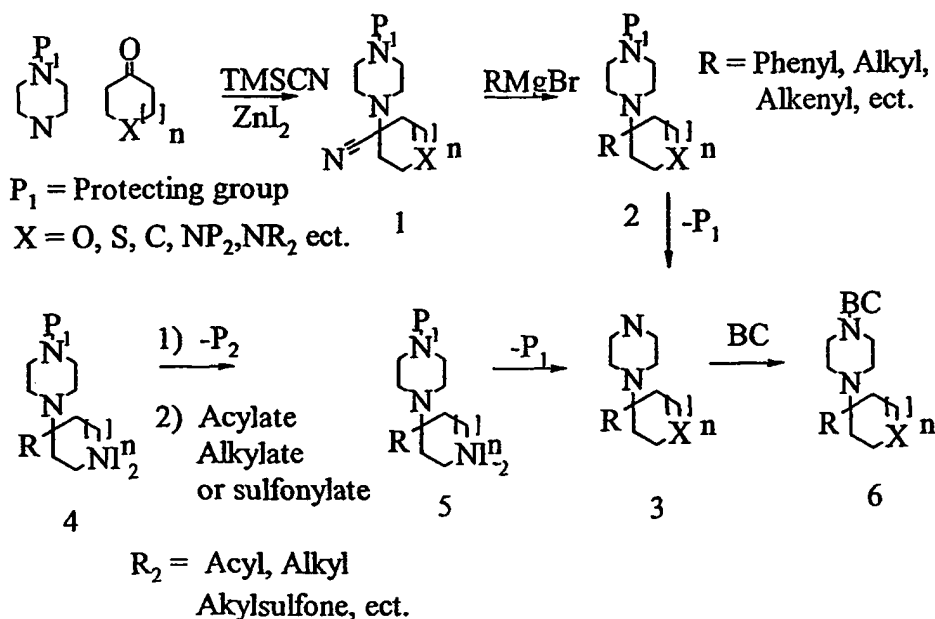
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functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid. Removal of BOC protecting groups is carried out in a solvent such as DCM, methanol, or ethyl acetate, with a strong acid, such as TFA, HCl, or HCl gas.

- 5 However prepared, the compound of formula I, when existing as a diastereomeric mixture, may be separated into diastereomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically
- 10 active acid as a resolving agent. Alternatively, any enantiomer of a compound of the formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration. Additionally, any enantiomer of a compound may be separated by chiral chromatography.

- The A domains of the present invention, in general, may be prepared from
- 15 commercially available starting materials via known chemical transformations. For example, a synthesis of certain A domains of the present invention is illustrated below in Schemes 1-2 below.

Scheme 1

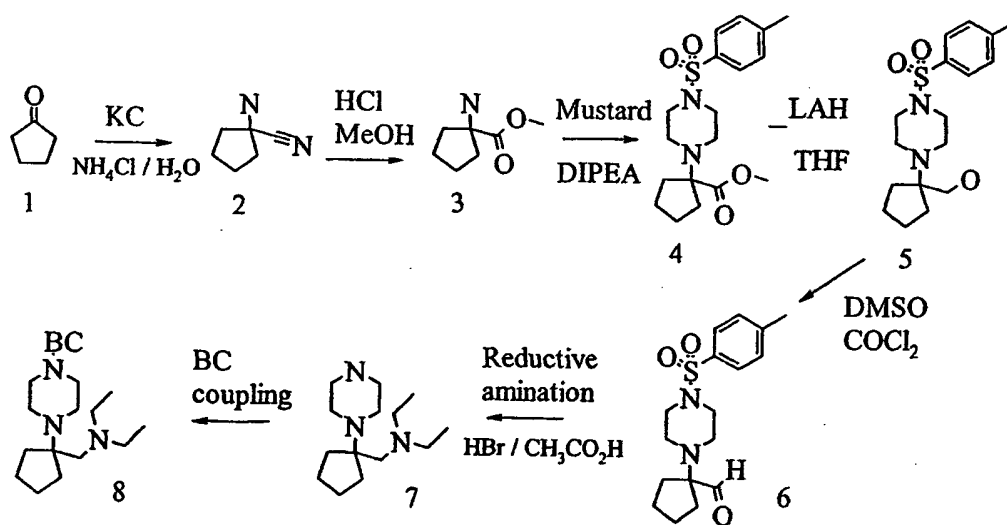


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Scheme 1 shows a protocol to afford the A-domains of certain compounds of formula (I). According to Scheme 1, synthesis begins with the formation of the -amino nitrile of general structure 1 from a mono-protected piperazine and the appropriate cyclic ketone, for example cyclopentanone. R₁ is introduced via an alkyl magnesium halide, which can be prepared by standard literature protocols, to yield compounds of type 2 and 4. Compounds of type 4 can be differentially de-protected and functionalized to yield compounds of general structure 5 where R₂ can be alkyl amide, sulfonamide or alkyl. Compounds of type 2 and 5 were deprotected by standard acid or palladium catalyzed protocols to yield compounds of general structure 3. By procedure common in the art, compounds of type 3 were coupled via an amide bond to yield melanocortin modulators of general structure 6.

Other A-domains of compounds of formula I are obtained following the protocol of Scheme 2.

15 Scheme 2



Compounds of formula (I) having the structure (8) or compounds derivable from (8) can be prepared as outlined in scheme 2. Compound 2 is prepared from the cyclic ketone 1 under classical Strecker conditions, which is then hydrolyzed and esterified with methanolic hydrochloric acid to yield compound 3. The piperazine ring of 4 is generated from a mustard and DIPEA. Compound 4 can then be reduced with LAH to yield the alkyl alcohol of 5. Compound 5 is then oxidized under Swern-oxidation conditions to

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yield 6. Reductive amination with diethyl amine followed by deprotection of the piperazine yields compound 7. By procedure common in the art, compound 7 was coupled via an amide bond to "BC" domain piece to yield melanocortin modulator of type 8.

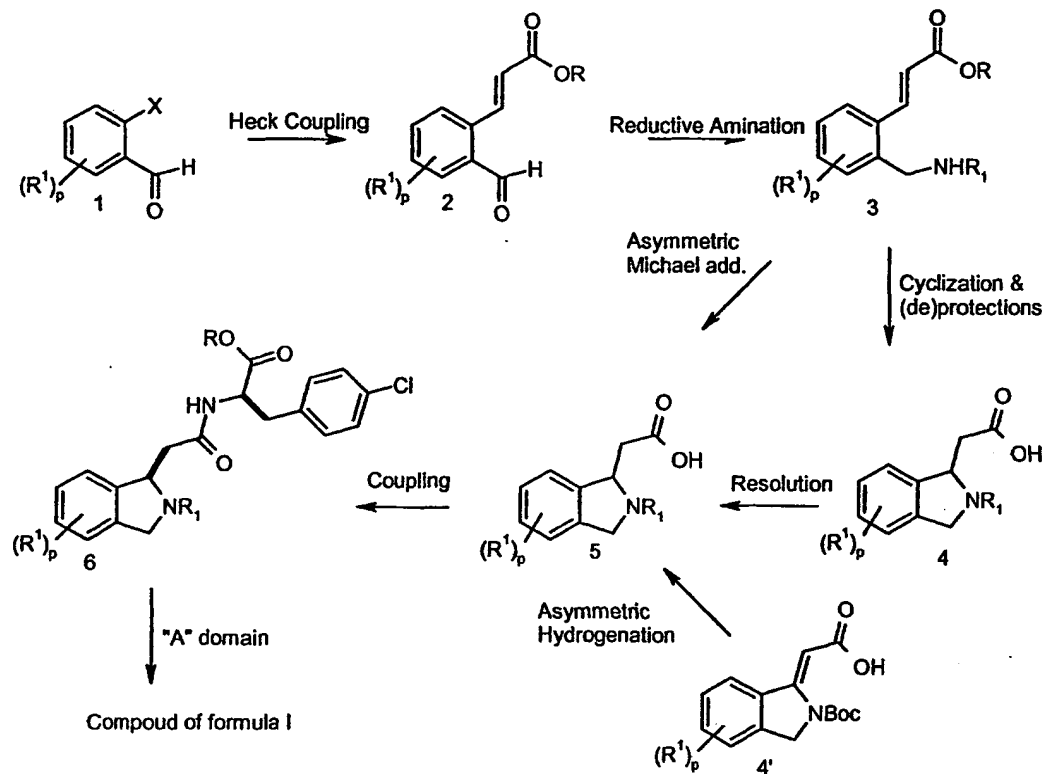
5 Chiral resolution of a racemic "A" piece may be accomplished by chiral chromatography wherein the faster eluting isomer(s) are labeled isomer 1 and the next eluting isomer 2. Methods and protocols for chiral chromatography and other resolution methods are disclosed herein or known to one of skill in the art.

10 The "B" domain piece as used herein may be purchased or prepared from readily available starting materials. A preferred "B" domain piece is 4-chloro-D-Phenylalanine available commercially or by resolution of commercial racemic mixtures. The "B" domain may be coupled to an "A" domain which is then coupled to a "C" domain or the "B" domain may be coupled first to a "C" domain to form a "BC" domain piece, which is then coupled to an "A" domain piece. Coupling procedures for the above reactions
15 were disclosed *supra*, and in the experimental section.

 The present invention also provides novel processes for preparing certain intermediates and/or compounds of the invention. For example a convergent synthesis of a key intermediate isoindoline (5) (see Scheme 3 below) via a Heck coupling, followed by a reductive amination, a ring cyclization and a resolution has been achieved. Also,
20 alternate asymmetric approaches including asymmetric Michael addition and asymmetric hydrogenation have been utilized to prepare compounds of the invention and/or intermediates thereof.

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Scheme 3



As shown in scheme 3, the isoindoline compounds of the present invention may be prepared from 2-halobenzaldehyde **1** or substituted analog thereof (scheme 3). Preferred starting material is 2-bromobenzaldehyde or substituted analog thereof. Pd-mediated Heck coupling of 2-bromobenzaldehydes **1** with for example, methyl acrylate, provided β -unsaturated methyl esters **2**, which undergoes reductive amination to give amines (or carbamates where R_1 is for example, Boc) **3**. Various Heck coupling reagents and conditions were found suitable to effect the coupling reaction. Useful catalyst and ligands include $Pd(OAc)_2/PPh_3/Et_3N$, $Pd(OAc)PPh_3/BU_4NBr$, $Pd(PPh_3)_2Cl_2/CuI$, $Pd(OAc)_2/P(O-Tol)_3$. Suitable solvent or solvent systems for the Heck coupling reaction include DMF, toluene and ethyl acetate. Most preferred base is triethylamine.

Reductive amination of the aldehyde functionality of **2** to amines is accomplished in good yields by reaction with benzylamine or -methylbenzylamine in acidic conditions, followed by *in situ* reduction of the incipient imines with $NaCNBH_3$ at about pH 5. Other reducing agents including $Na(OAc)_3BH$ and $NaBH_4/H$ may also be used to effect

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reduction of the incipient imines. Interestingly, the resulting amines immediately cyclized to the isoindoline compounds under the same acidic conditions for the reduction.

Since the N-Boc group is part of certain target molecules of the invention, direct preparation of compound 4 may also be effected by use of BocNH₂ instead of benzylamine in the reductive amination step. Screening of various reducing agents demonstrated that the combination of Et₃SiH and TFA in CH₃CN represents the preferred method for effecting reductive amination using BocNH₂.

The *N*-Boc isoindolinecarboxylic acid 5 may also be prepared from 3 as the carbamate, by an intra-molecular Michael addition and ester hydrolysis. The resolution of the isoindolinecarboxylic acids 4 by crystallization afforded enantio-pure compounds 5.

Two alternate asymmetric approaches have also been developed for the synthesis of isoindolinecarboxylic acid 5 i.e. asymmetric Michael additions and asymmetric hydrogenation. In the asymmetric Michael addition approach, *N*-methylbenzyl amine is used as a chiral auxiliary to induce the enantio-selectivity. In the asymmetric hydrogenation approach, compound 4' could be converted to 5 stereoselectively in the presence of chiral ligands.

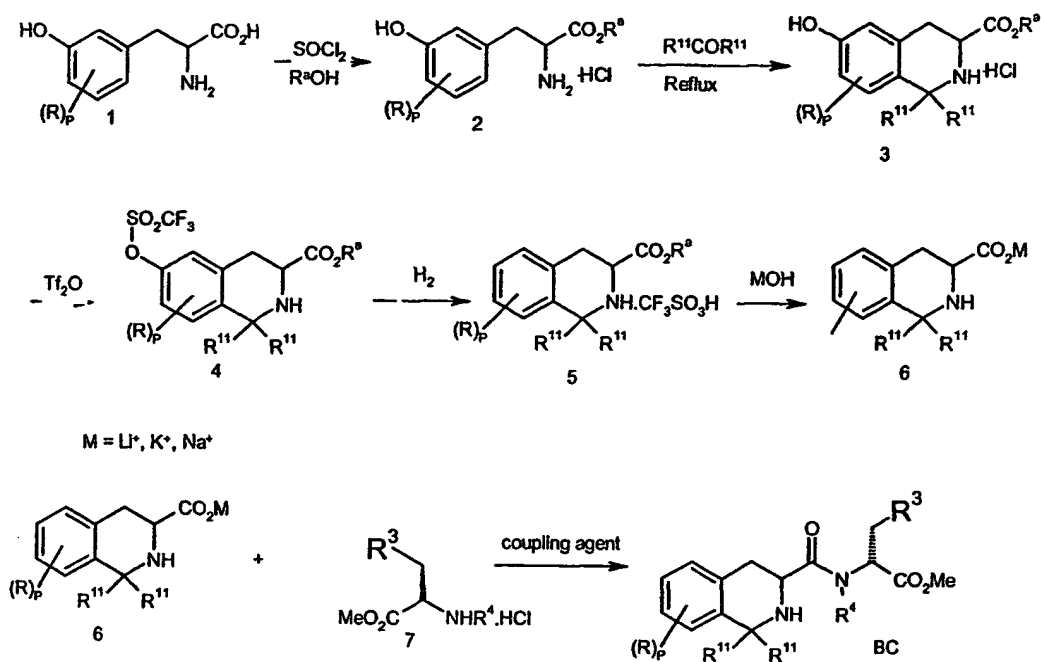
Finally the coupling of the isoindolines 5 with the "B" domain piece, i.e. D-Cl-Phe to afford compound 6 ("BC" piece) is accomplished by standard amino acid coupling reactions such as, for example, by the use of EDC or EDCI or other activating agents in the presence of suitable base such as for example, dimethylaminopyridine (DMAP). The product (6) is then coupled with an "A" domain piece such as for example, 4-benzyl-4-bromo-1-methylpiperidiny l piperazine (compound 3D), as discussed herein to afford the target MC4R agonist compound of formula I by coupling reactions known to one of skill in the art.

Preferably, the isoindole or other "C" domain piece is coupled to an "AB" coupled domain piece to form the compound of formula I.

Compound of formula I having the isoquinoline functionality in the "C" domain may be prepared following Scheme 4 below, or modifications thereof:

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Scheme 4



- 5 As shown in Scheme 4, m-tyrosine ester or analogs, including substituted analogs thereof, may be esterified by forming the acid halide followed by nucleophilic displacement the group OR⁻ from an alcohol, i.e. methanol or ethanol. Where thionyl chloride or other halide source is used the product may be isolated as the acid addition salt (2). The resulting ester (2) is subjected to a Pictet-Spengler reaction by heating with a
- 10 suitable ketone or aldehyde in refluxing conditions. For example, an unsubstituted isoquinoline backbone (3) may be formed by employing formaldehyde in the pictet-Spengler reaction. On the other hand, a gem-dimethyl substituted isoquinoline wherein R¹¹ is methyl, may be formed by using acetone as the ketone source and solvent. The product isoquinoline (3) may be isolated preferably as the acid addition salt. Where
- 15 m-tyrosine is used as the starting material, the free hydroxyl group is removed first by protection/activation with a good leaving group such as, for example, reaction with triflic anhydride (trifluoromethane sulfonic anhydride) or methanesulfonic acid to form the triflate or mesylate in the presence of a base. The triflate is a preferred group used to set up the compound (3) for deoxygenation because of the extra electron withdrawing effect
- 20 of the trifluoromethane substituent. The deoxygenation reaction is effected by

hydrogenation at pressures of about 50psi. The product (4) may be isolated as the acid addition salt. The product (4) is hydrolyzed under basic conditions to afford the acid salt. Suitable bases for the above hydrolysis include aqueous sodium hydroxide, potassium hydroxide and lithium hydroxide. The reaction is preferably performed in a mixture of aqueous and organic solvents. An exotherm during addition of base may be regulated (i.e. less than about 35 °C) to avoid overheating or "runaway reactions." The reaction product may be isolated by aqueous work up. Alternatively, the entire mixture may be concentrated and washed with organic solvents to afford the desired product (6) after crystallization.

10 The product (6) is then reacted with a "B" domain substrate such as, for example, 4-chloro-D-phenylalanine as described previously and in the experimental section. The resulting "BC" combination product is then reacted with an "A" domain such as, for example, diethyl-(2-phenyl-2-piperazin-1-yl-ethyl)-amine to form the respective compound of formula I. Alternatively, the product (6) may be reacted with an "AB" domain combination product to afford a compound of formula I.

15 One of skill is aware that certain protections and deprotections of intermediates in Scheme 4, to form the carbamate, substituted amine or free amine at the isoquinolinyl nitrogen are possible and contemplated as within the scope of this invention. Unless otherwise specified, reagents and procedures for effecting the reactions described herein are known to one of skill in the art and may be found in general reference texts such as *Advanced Organic Chemistry* by J. March, 5th edition, Wiley Interscience Publishers, New York, NY, and references therein.

20 In an alternate procedure, the isoquinoline product i.e. compound (3) or (5) including their protected analogs may be resolved by reaction with a resolving agent such as for example, L-tartaric acid, dehydroabietylamine or other resolving agents known to one of skill in the art.

25 Alternatively, asymmetric analogs of product (6) may be prepared by using asymmetric starting materials. For example, L-DOPA may be used in place of m-tyrosine ester in reactions essentially similar to those described and illustrated in Scheme 4, and in the examples to afford the asymmetric analog of compound (6).

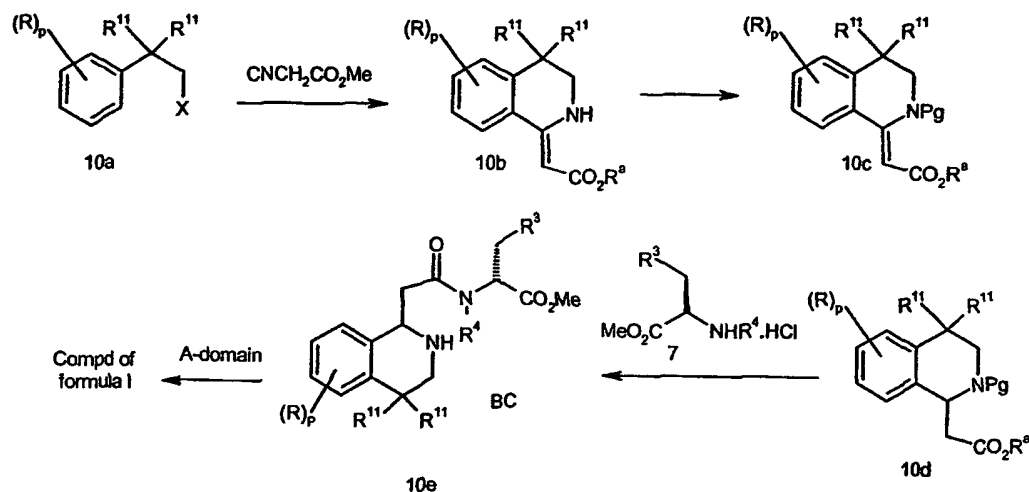
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Tetrahydroisoquinoline acetic acid derivates may be prepared and utilized as shown in Scheme 10a below:

Scheme 10a

5



As shown in Scheme 10a, a compound of formula 10a wherein X is halogen, preferably bromo or chloro, and R and R^{11} are as defined previously, and which is obtained commercially or prepared from commercial starting materials is reacted with cyanomethylethylacetate to afford a compound of formula 10b. The compound of formula 10b may be protected as the compound 10c with a suitable protecting group (Pg) and then subjected to hydrogenation conditions including for example asymmetric hydrogenation to form a compound of formula 10d which may be chiral (depending on hydrogenation conditions, i.e. asymmetric versus non-asymmetric hydrogenation). The compound of formula 10d or stereoisomer thereof, is reacted with a B-domain piece such as, for example, 4-chloro-D-phe to afford a BC piece (10e). The compound of formula 10e is then reacted with an A-domain piece to afford a compound of formula I. The details of the specific reaction steps are similar to or analogous to reactions taught herein, and in the experimental section. Furthermore, one of skill in the art is aware of that such intermediate reactions as hydrolysis and deprotection may be necessary to achieve optimum yields in certain steps of the scheme as shown. One of skill in the art is also aware of further common manipulations such as N-alkylation or acylation, and alkylations on the benzene ring to afford other compounds of formula I.

Formulation

The compound of formula I is preferably formulated in a unit dosage form prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical composition comprising a compound of formula I and one or more
5 pharmaceutically acceptable carriers, diluents or excipients.

The present pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (formula I compound) will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of
10 a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile
15 injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc,
20 magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

25

Dose

The specific dose administered is determined by the particular circumstances surrounding each situation. These circumstances include, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being
30 treated, the severity of the condition/symptom being treated, and the age and sex of the recipient. However, it will be understood that the appropriate caregiver in light of the

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particular circumstances of the patient or recipient will determine the therapeutic dosage administered.

Generally, an effective minimum daily dose of a compound of formula I is about 1, 5, 10, 15, or 20 mg. Typically, an effective maximum dose is about 500, 100, 60, 50, or 40 mg. The exact dose may be determined, in accordance with the standard practice in the medical or veterinary arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the dose until the desired therapeutic effect is observed.

10 Route of Administration

The compounds may be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes.

Combination Therapy

15 Compounds of Formula I may be used in combination with other drugs that are used in the treatment of the diseases or conditions for which compounds of formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of formula I. When a compound of formula I is used contemporaneously with one or more other drugs, a
20 pharmaceutical composition containing such other drugs in addition to the compound of formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of formula I. Examples of other active ingredients that may be combined with a compound of formula I, either administered separately or in the same
25 pharmaceutical compositions, include, but are not limited to:

- (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin;
- 30 (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide;
- (d) alpha glucosidase inhibitors (such as acarbose),

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- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic alcohol nicotinic acid or a salt thereof, (iv) proliferator-
5 activator receptor alpha agonists such as fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzaifibrate), (v) inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide, (vi) probucol, (vii) vitamin E, and (viii) thyromimetics;
- (f) PPAR δ agonists such as those disclosed in WO97/28149;
- 10 (g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, and other beta-3 adrenergic receptor agonists such as those described in U.S. Patent Application No.'s 60/217,965, 60/241,614 and 60/247,304;
- (h) feeding behavior modifying agents such as neuropeptide Y antagonists (e.g. neuropeptide Y5) such as those disclosed in WO 97/19682, WO 97/20820, WO
15 97/20821, WO 97/20822 and WO 97/20823;
- (i) PPAR alpha agonists such as described in WO 97/36579 by Glaxo;
- (j) PPAR γ antagonists as described in WO97/10813;
- (k) serotonin reuptake inhibitors such as fluoxetine and sertraline;
- (l) growth hormone secretagogues such as MK-0677; and
- 20 (m) agents useful in the treatment of male and/or female sexual dysfunction such as phosphodiester V inhibitors such as sildenafil and ICI-351, and alpha-2 adrenergic receptor antagonists, such as phentolamine mesylate; and dopamine-receptor agonists, such as apomorphine.

25 Demonstration of Function:

A. Binding Assay.

The radioligand binding assay is used to identify competitive inhibitors of ¹²⁵I-NDP-alpha-MSH binding to cloned human MCRs using membranes from stably transfected human embryonic kidney (HEK) 293 cells.

- 30 HEK 293 cells transfected with human or rat melanocortin receptors are grown either as adherent monolayers or suspension culture. Monolayer cells are grown in roller

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bottle cultures at 37°C and 5% CO₂/air atmosphere in a 3:1 mixture of Dulbecco's modified Eagle medium (DMEM) and Ham's F12 containing 25 mM L-glucose, 100 units/ml penicillin G, 100 microgram/ml streptomycin, 250 nanogram/ml amphotericin B, 300 microgram/ml gentamicin and supplemented with 5% fetal bovine serum. Monolayer
5 cells are adapted to suspension culture (Berg et al., Biotechniques Vol. 14, No. 6, 1993) and are grown in spinner or shaker flasks (37°C and 7.5% CO₂/air overlay) in a modified DME/F12 medium containing 0.1 mM CaCl₂, 2% equine serum and 100 microgram/ml sodium heparin (to prevent cell-cell aggregation). Cells are harvested by centrifugation, washed in PBS, and pellets are stored frozen at -80°C until membrane preparations.

10 The cell pellets are resuspended in 10 volumes of membrane preparation buffer (*i.e.*, 1 g pellet to 10 ml buffer) having the following composition: 50 mM Tris pH 7.5 @ 4°C, 250 mM sucrose, 1 mM MgCl₂, Complete® EDTA-free protease inhibitor tablet (Boehringer Mannheim), and 24 micrograms/ml DNase I (Sigma, St. Louis, MO). The cells are homogenized with a motor-driven dounce using 20 strokes, and the homogenate
15 is centrifuged at 38,000 x g at 4°C for 40 minutes. The pellets are resuspended in membrane preparation buffer at a concentration of 2.5-7.5 mg/ml and 1 milliliter aliquots of membrane homogenates are quickly frozen in liquid nitrogen and then stored at -80°C.

Solutions of a compound of formula I (300 picomolar to 30 micromolar) or unlabelled NDP-alpha-MSH (1 picomolar to 100 nanomolar) are added to 150 microliters
20 of membrane binding buffer to yield final concentrations (listed in parentheses). The membrane binding buffer has the following composition: 25 mM HEPES pH 7.5; 10 mM CaCl₂; 0.3% BSA). One hundred fifty microliters of membrane binding buffer containing 0.5-5.0 microgram membrane protein is added, followed by 50 nanomolar
125I-NDP-alpha-MSH to final concentration of 100 picomolar. Additionally, fifty
25 microliters of SPA beads (5 mg/ml) are added and the resulting mixture is agitated briefly and incubated for 10 hours at room temperature. The radioactivity is quantified in a Wallac Trilux Microplate Scintillation counter. IC₅₀ values obtained in competition assays are converted to affinity constants (K_i values) using the Cheng-Prusoff equation:
$$K_i = IC_{50} / (1 + D/K_d).$$

30

B. Functional assays.

Functional cell based assays are developed to discriminate agonists and antagonists.

Agonist Assay: HEK 293 cells stably expressing a human melanocortin receptor
5 (see *e.g.*, Yang, et al., *Mol-Endocrinol.*, 11(3): 274-80, 1997) are dissociated from tissue culture flasks using a trypsin/EDTA solution(0.25%; Life Technologies, Rockville, MD). Cells are collected by centrifugation and resuspended in DMEM (Life Technologies, Rockville, MD) supplemented with 1% L-glutamine and 0.5% fetal bovine serum. Cells are counted and diluted to $4.5 \times 10^5/\text{ml}$.

10 A compound of formula I is diluted in dimethylsulfoxide (DMSO) (3×10^{-5} to 3×10^{-10} M final concentrations) and 0.05 volume of compound solution is added to 0.95 volumes of cell suspension; the final DMSO concentration is 0.5%. After incubation at $37^\circ\text{C}/5\% \text{ CO}_2$ for 5 hours, cells are lysed by addition of luciferin solution (50 mM Tris, 1 mM MgCl_2 , 0.2 % Triton-X100, 5 mM DTT, 500 micromolar Coenzyme A, 150
15 micromolar ATP, and 440 micromolar luciferin) to quantify the activity of the reporter gene luciferase, an indirect measurement of intracellular cAMP production.

Luciferase activity is measured from the cell lysate using a Wallac Victor 2 luminometer. The amount of lumen production which results from a compound of formula I is compared to that amount of lumens produced in response to NDP- alpha-
20 MSH, defined as a 100% agonist, to obtain the relative efficacy of a compound. The EC_{50} is defined as the compound concentration that results in half maximal stimulation, when compared to its own maximal level of stimulation.

Melanocortin Receptor Whole Cell cAMP Accumulation Assay Compound Preparation:

25 In the agonist assay, compounds are prepared as 10mM and NDP-aMSH (control) as 33.3 μM stock solutions in 100 % DMSO. These are serially diluted in 100 % DMSO. The compound plate is further diluted 1:200 in compound dilution buffer (HBSS-092, 1 mM Ascorbic Acid, 1 mM IBMX, 0.6% DMSO, 0.1% BSA). The final concentration range being 10 μM – 100 pM for compound and 33.33 nM – 0.3 pM for control in 0.5 %
30 DMSO. Transfer 20 μl from this plate into four PET 96-well plates (all assays are performed in duplicate for each receptor).

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Cell Culture and Cell Stimulation:

HEK 293 cells stably transfected with the MC3R and MC4R were grown in DMEM containing 10 % FBS and 1% Antibiotic/Antimycotic Solution. On the day of the assay the cells were dislodged with enzyme free cell dissociation solution and resuspended in cell buffer (HBSS-092, 0.1% BSA, 10 mM HEPES) at 1×10^6 cells/ml. Add 40 μ l of cells/well to the PET 96-well plates containing 20 μ l diluted compound and control. Incubate @ 37°C in a waterbath for 20 minutes. Stop the assay by adding 50 μ l Quench Buffer (50 mM Na Acetate, 0.25% Triton X-100).

Radioligand Binding Assays:

Radioligand binding assays were run in SPA buffer (50mM Sodium Acetate, 0.1% BSA). The beads, antibody and radioligand were diluted in SPA buffer to provide sufficient volume for each 96-well plate. To each quenched assay well was added 100 μ l cocktail containing 33.33 μ l of beads, 33.33 μ l antibody and 33.33 μ l 125 I-cAMP. This was based on a final concentration of 6.3 mg/ml beads, 0.65 % anti-goat antibody and 61 pM of 125 I-cAMP (containing 25000-30000 CPM) in a final assay volume of 210 μ l. The plates were counted in a Wallac MicroBeta counter after a 12-hour incubation.

The data was converted to pmoles cAMP using a standard curve assayed under the same conditions. The data was analyzed using Activity Base software to generate agonist potencies (EC_{50}) and percent relative efficacy data to NDP-aMSH.

C. In vivo food intake models.

1) Overnight food intake. Sprague Dawley rats are injected intracerebroventricularly with a test compound in 400 nL of 50% propylene glycol/artificial cerebrospinal fluid one hour prior to onset of dark cycle (12 hours). Food intake is determined using a computerized system in which each rat's food is placed on a computer monitored balance. Cumulative food intake for 16 hours post compound administration is measured.

2) Food intake in diet induced obese mice. Male C57/B16J mice maintained on a high fat diet (60% fat calories) for 6.5 months from 4 weeks of age are dosed intraperitoneally with a compound of formula I. Food intake and body weight are

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measured over an eight day period. Biochemical parameters relating to obesity, including leptin, insulin, triglyceride, free fatty acid, cholesterol and serum glucose levels are determined.

5 D. Rat Ex Copula Assay.

Sexually mature male Caesarian Derived Sprague Dawley (CD) rats (over 60 days old) are used with the suspensory ligament surgically removed to prevent retraction of the penis back into the penile sheath during the ex copula evaluations. Animals receive food and water *ad lib* and are kept on a normal light/dark cycle. Studies are conducted during
10 the light cycle.

1) Conditioning to Supine Restraint for Ex Copula Reflex Tests. This conditioning takes about 4 days. Day 1, the animals are placed in a darkened restrainer and left for 15 - 30 minutes. Day 2, the animals are restrained in a supine position in the restrainer for 15 - 30 minutes. Day 3, the animals are restrained in the supine position
15 with the penile sheath retracted for 15 - 30 minutes. Day 4, the animals are restrained in the supine position with the penile sheath retracted until penile responses are observed. Some animals require additional days of conditioning before they are completely acclimated to the procedures; non-responders are removed from further evaluation. After any handling or evaluation, animals are given a treat to ensure positive reinforcement.

20 2) Ex Copula Reflex Tests. Rats are gently restrained in a supine position with their anterior torso placed inside a cylinder of adequate size to allow for normal head and paw grooming. For a 400-500 gram rat, the diameter of the cylinder is approximately 8 cm. The lower torso and hind limbs are restrained with a non-adhesive material (vetrap). An additional piece of vetrap with a hole in it, through which the glans penis
25 will be passed, is fastened over the animal to maintain the preputial sheath in a retracted position. Penile responses will be observed, typically termed *ex copula* genital reflex tests. Typically, a series of penile erections will occur spontaneously within a few minutes after sheath retraction. The types of normal reflexogenic erectile responses include elongation, engorgement, cup and flip. An elongation is classified as an
30 extension of the penile body. Engorgement is a dilation of the glans penis. A cup is defined as an intense erection where the distal margin of the glans penis momentarily flares open to form a cup. A flip is a dorsiflexion of the penile body.

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Baseline and/or vehicle evaluations are conducted to determine how and if an animal will respond. Some animals have a long duration until the first response while others are non-responders altogether. During this baseline evaluation, latency to first response time, number and type of responses are recorded. The testing time frame is 15 minutes after the first response.

After a minimum of 1 day between evaluations, these same animals are administered a compound of formula I at 20 mg/kg and evaluated for penile reflexes. All evaluations are videotaped and scored later. Data are collected and analyzed using paired 2 tailed t-tests to compared baseline and/or vehicle evaluations to drug treated evaluations for individual animals. Groups of a minimum of 4 animals are utilized to reduce variability.

Positive reference controls are included in each study to assure the validity of the study. Animals can be dosed by a number of routes of administration depending on the nature of the study to be performed. The routes of administration includes intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and intracerebral ventricular (ICY).

E. Models of Female Sexual Dysfunction.

Rodent assays relevant to female sexual receptivity include the behavioral model of lordosis and direct observations of copulatory activity. There is also a urethrogenital reflex model in anesthetized spinally transected rats for measuring orgasm in both male and female rats. These and other established animal models of female sexual dysfunction are described in McKenna, et al., *Am. J. Physiol.*, (Regulatory Integrative Comp. Physiol 30):R1276-R1285, 1991; McKenna, et al., *Pharm. Bioch. Behav.*, 40:151-156, 1991; and Takahashi, et al., *Brain Res.*, 359:194-207, 1985.

Sample assay results for compounds of the invention is provided in the results table below:

Results

Compound	MC4 Ki (nM)	MC4 EC ₅₀ (nM)	% Rel. Eff.
5I	9	4.3	104
4I	24.3	18.9	114
8I	28.8	99.8	124
10I	6.5	25.4	112

Experimental Section

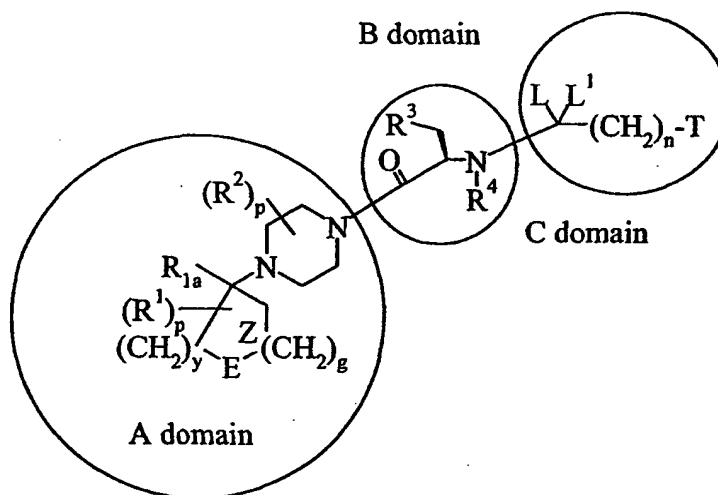
The following abbreviations have been used in this application for brevity.

5	BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
	Boc	t-butoxycarbonyl
	CBZ	benzyloxycarbonyl
	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
10	DIPEA	diisopropylethylamine (also DIEA)
	DMAP	4-dimethylamino pyridine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
	eq.	equivalent(s)
15	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl
	ESI-MS	electron spray ion-mass spectroscopy
	Et	ethyl
	EtOAc	ethyl acetate
	HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N' tetramethyluronium
20		hexafluorophosphate
	HOAT:	1-hydroxy-7-azabenzotriazole
	HOBT	1-hydroxybenzotriazole hydrate
	HPLC	high performance liquid chromatography
	HRMS	high resolution mass
25	MS	mass spectroscopy
		LRMS low resolution mass
	Me	methyl
	Ms	methylsulfonyl
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)-dipalladium(0)
30	Ph	phenyl
	Phe	phenylalanine
	Pr	propyl

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TBS	tertbutyldimethylsilyl
TFA	trifluoroacetic acid
TEA	triethylamine
THF	tetrahydrofuran
5 Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TLC	thin-layer chromatography
h	hour
rt	room temperature also r.t. or RT

- 10 The following experimentals describe the synthesis of mc4 agonists of formula I of the motif below. In general B and C pieces were prepared as described and coupled to form coupled B-C pieces (see preparations BC1 to BC18 for example). The B-C coupled pieces were in turn coupled to A-pieces prepared as described infra.



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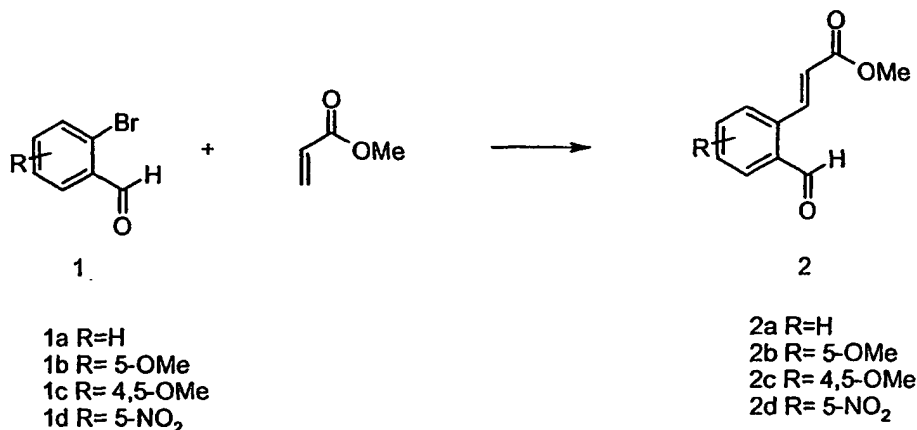
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Preparation of Novel C-Domain Pieces

Heck Coupling

Preparation PP1

Synthesis of Compound (2a) by a Heck Coupling of 2-bromobenzaldehyde (1a) with
Methyl Acrylate ($\text{Pd}(\text{OAc})_2/\text{PPh}_3$ as the catalyst)



A mixture of 2-bromobenzaldehyde (1a) (24.5 g, 132 mmol), methyl acrylate (17.9 mL, 199 mmol), $\text{Pd}(\text{OAc})_2$ (590 mg, 2.65 mmol, 2 mol%), PPh_3 (1.39 g, 5.30 mmol, 4 mol%) and Et_3N (46 mL, 331 mmol) was stirred at 80 °C for 15 h. Large amount of yellow solid was formed after the reaction was done. The mixture was cooled to rt, concentrated, and mixed with H_2O (200 mL). The organic solid was collected by filtration, and then applied to a plug of silica gel (25 g) (EtOAc /hexane 1:1) to give a dark yellow solid. The solid was purified by crystallization (100 mL EtOAc bottom layer, 120 mL hexane top layer) to provide 17.57 g (70%) (100 % pure by NMR) of the first crop and 5.23 g (21%) (95% by NMR) of the second crop of 2a.

Preparation PP2

Synthesis of Compound (2a) by a Heck Coupling of 2-bromobenzaldehyde (1a) with
Methyl Acrylate (R = H) ($\text{Pd}(\text{OAc})_2/\text{P}(\text{O-Tolyl})_3$ as the catalyst)

Compound 1a (9.998 g, 54.04 mmol) was dissolved in toluene (20 mL) at RT. Methylacrylate (5.996 g, 69.65 mmol, 1.29 eq.), NEt_3 (15 mL), $\text{Pd}(\text{OAc})_2$ and $\text{P}(\text{O-Tolyl})_3$ were successively added and the mixture was stirred under reflux. After 2 hours, the reaction mixture was allowed to cool to RT. Then the precipitated yellow catalyst

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was removed by filtration. The catalyst was rinsed with toluene (2 X 10 mL) and the filtrates were concentrated to dryness under reduced pressure. The residual oil was dried under vacuum over the weekend to give a crude solid (11.449 g). The solid was taken-up with isopropanol (25 mL) and stirred overnight at RT. Then, the precipitate was filtered and rinsed with isopropanol (5 mL). The wet cake (8.240 g) was dried overnight at RT affording the highly pure 2-carboxaldehyde-methyl-cinnamate with 74% yield (7.627 g, 40.1 mmol).

Preparation PP3

10 Heck Coupling of 1b and Methyl Acrylate to Form 2b (R = 5-OMe)

A mixture of 2-bromo-5-methoxybenzaldehyde (1b) (4.5 g, 20.9 mmol, Aldrich), methyl acrylate (2.7 g, 1.5 eq, 2.83 mL), Et₃N (7.4 g, 3.5 eq, 10.2 mL), Pd(OAc)₂ (93 mg, 0.02 eq), and P(O-Tol)₃ was stirred and heated to 80°C over 2-3 days. The reaction mixture was cooled to RT, partitioned between EtOAc (50 mL) and brine (50 mL). The aqueous was extracted with EtOAc (2x50 mL). The combined organic was washed with brine (1x50 mL), dried over MgSO₄, filtered, concentrated to yield a yellow brown oil (5.01 g, 109 %). This crude oil was purified in a hot solvent Hex / EtOAc (80 mL/ 15 mL) to yield 2b as a pale yellow solid (3.5 g, 76 %).

20

Preparation PP4

Heck Coupling of 1c and Methyl Acrylate to Form 2c (R = 4,5-OMe)

To a solution of 1c (906 mg, 3.70 mmol) in toluene (2 mL) was added Pd(OAc)₂ (17 mg, 0.074 mmol, 2 mol%), P(O-Tolyl)₃ (45 mg, 0.148 mmol, 4 mol%), methyl acrylate (0.5 mL, 5.55 mmol) and Et₃N (1.5 mL, 11.1 mmol). The mixture was stirred at 80 °C for 21 h, cooled to rt, and mixed with H₂O (40 mL). The organic compounds were extracted with EtOAc (50 mL), washed with brine (40 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography to provide 466 mg (47%) of recovered 1c followed by 450 mg (49%) of 2c (4,5-Ome).

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Preparation PP5Heck Coupling of 1d and Methyl Acrylate to Form 2d (R = 5-NO₂)

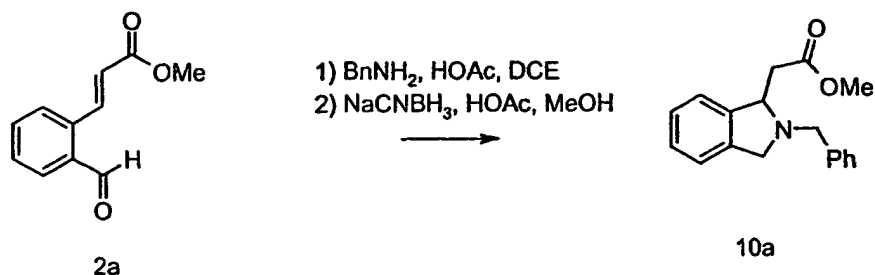
The procedure is same as that of 2c, yielding 82% of 2d after purification.

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Reductive Amination

Preparation PP6

Reductive amination of (2a) with benzyl amine to form isoindoline (10a)



10

To a solution of 2a (11.27 g, 59.2 mmol) in ClCH₂CH₂Cl (60 mL) was added BnNH₂ (6.47 mL, 59.2 mmol), followed by HOAc (5.1 mL, 89 mmol). The mixture was stirred at rt for 1 h. NaCNBH₃ (5.58 g, 88.8 mmol) and MeOH (30 mL) were then added to the above solution. The resulting mixture was stirred at rt for another 2 h and

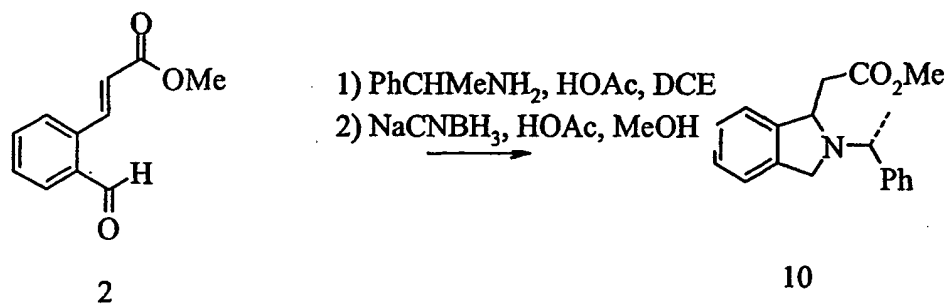
15 quenched with sat. NaHCO₃ solution (150 mL). The mixture was extracted with EtOAc (2 × 100 mL) and the combined organic layers were washed with brine (150 mL), dried (Na₂SO₄), and concentrated to provide 15.3 g of crude product of 10a which was carried out for the next hydrogenolysis reaction.

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Preparation PP7

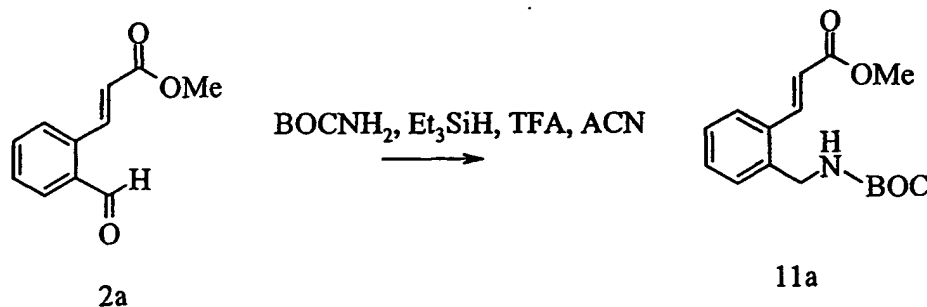
One-pot process from 2-carboxaldehyde-methyl-cinnamate to target cyclized isoindoline product using NaBH_3CN



2-carboxaldehyde-methyl-cinnamate **2a** (3.254 g, 17.1 mmol) was dissolved in a 1:1 MeOH: PhCH_3 mixture (20 mL) at RT. R-(+)-phenethylamine (2.073 g, 17.1 mmol) was added and the solution was heated under reflux for 2 hours. HPLC in process control indicated that the imine formation was completed. Then, AcOH (2.055 g, 34.2 mmol) and NaBH_3CN (2.15 g, 34.2 mmol) were successively added at RT, the reaction mixture being cooled with a water-bath. The reaction mixture was post-agitated overnight. Water (10 mL), MeOH (20 mL) and 37% HCl (2.8 mL) were successively added and the organic layer was extracted. The aqueous layer was washed with PhCH_3 (10 mL). Then, the aqueous layer was made basic with 5N NaOH (20 mL) and MeOH was concentrated to partly remove MeOH. Extraction with EtOAc (2X 25 mL) was performed. The combined organic layers were dried over MgSO_4 , filtered and rinsed with EtOAc (10 mL). The filtrates were concentrated under reduced pressure and the residual oil was dried under vacuum overnight at RT to afford the target cyclized isoindoline product **10b** with 92% yield (4.642 g, 15.7 mmol). HPLC % area indicated that the 2 diastereomers were produced in a 55:45 ratio. ^1H NMR confirmed this result by integration of the methyl group of the phenethyl substituent.

Note: The Heck or Heck-type coupling was performed in toluene with a slight excess of methylacrylate which was removed by distillation before the MeOH and the R-(+)-phenethylamine addition.

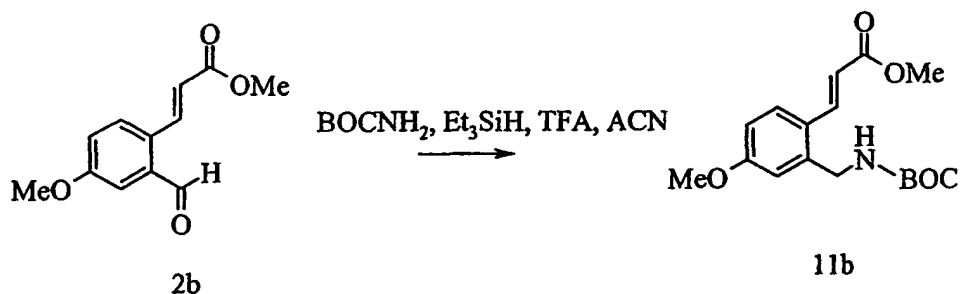
-75-

Preparation PP8Reductive amination of (2a) with *t*-butyl carbamate to form (11a)

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To a solution of aldehyde 2a (238 mg, 1.25 mmol) in CH₃CN (8 mL) was added *t*-butyl carbamate (439 mg, 3.75 mmol), followed by triethylsilane (0.6 mL, 3.75 mmol) and TFA (0.19 mL, 2.5 mmol). The mixture was stirred at rt overnight, quenched with sat. NaHCO₃ solution (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to provide 317 mg (87%) of 11a.

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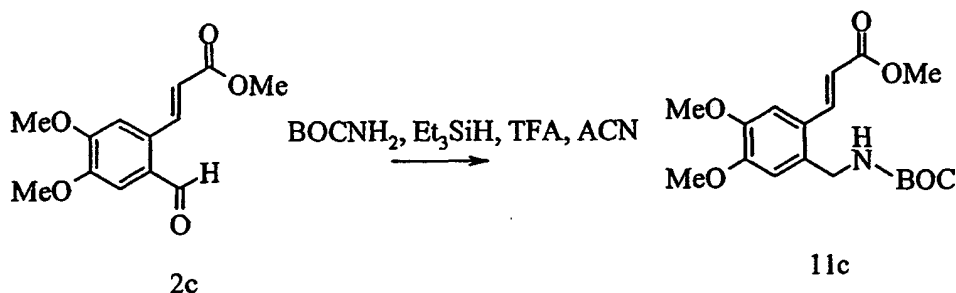
Preparation PP9Reductive amination of 2b with *t*-butyl carbamate to form 11b

15

A mixture of aldehyde 2b (600 mg, 2.72 mmol) Et₃SiH (955 mg, 3 eq, 1.31 mL), TFA (620 mg, 2 eq, 420 uL), *t*-butyl carbamate (980 mg, 3 eq) in acetonitrile (15 mL) was stirred at room temperature over 2 days. Removed the solvent on a Rotary evaporator and purified the crude residue on a flash column (100 g SiO₂, 7:1 → 6:1 Hex / EtOAc). Collected 307 mg good desired product 11b (35 %); 195 mg product contaminated with aldehyde SM (22 %).

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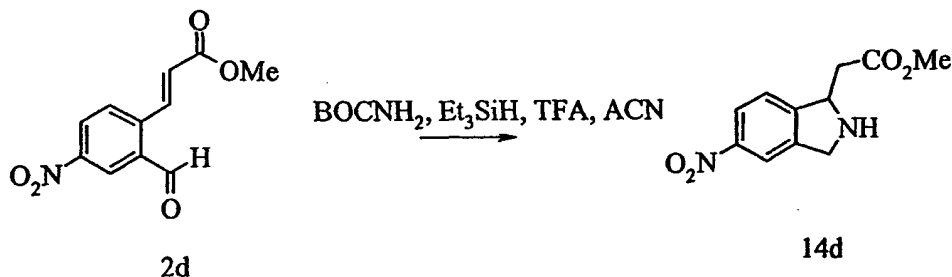
-76-

Preparation PP10Reductive amination of (2c) with *t*-butyl carbamate to form (11c)

- 5 To a solution of aldehyde 2c (411 mg, 1.64 mmol) in CH₃CN (10 mL) was added *t*-butyl carbamate (580 mg, 4.93 mmol), followed by triethylsilane (0.8 mL, 4.93 mmol) and TFA (0.25 mL, 3.28 mmol). The mixture was stirred at rt overnight, quenched with sat. NaHCO₃ solution (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:1, hexane/EtOAc 1:1) to provide 535 mg (93%) of 11c.
- 10

Preparation PP11

Synthesis of 14d



- 15 To a solution of 2d (1.02 g, 4.34 mmol) in CH₂Cl₂/CH₃CN (1:1 24 mL) was added BocNH₂ (1.5 g, 13.02 mmol), Et₃SiH (2.1 mL, 13.02 mmol), and TFA (0.67 mL, 8.67 mmol). The mixture was stirred at rt for 7 h. A precipitate was formed during the reaction. The reaction mixture was quenched with sat. NaHCO₃ solution (30 mL), and diluted with CH₂Cl₂ (40 mL). The organic layer was washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography
- 20

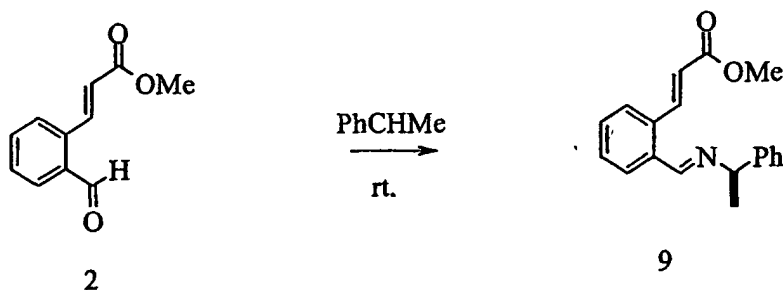
-77-

(hexane/EtOAc 3:1, then CH₂Cl₂/EtOAc 10:1) to provide 2.08 g yellow solid which still containing BocNH₂. The product is not the desired Boc-carbamate 14d. LC-MS result showed that the product is the Schiff base intermediate.

To the above product (420 mg) in CH₂Cl₂ (10 mL) was added Et₃SiH (1 mL) and TFA (0.4 mL). The mixture was stirred at rt for 1 h and small amount of sample was taken for NMR. NMR analysis demonstrated that the starting material was consumed and the product was 14d. TFA (0.7 mL) was then added to the above mixture and the resultant solution was stirred at rt for another 5 h and concentrated. The residue was dissolved in EtOAc (20 mL) and washed with H₂O (10 mL). The aqueous layer was basified with sat. NaHCO₃ (30 mL) and the organic compounds were extracted with CH₂Cl₂ (2 X 25 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated to provide 218 mg of the cyclized compound 14d.

Preparation PP12

Condensation of 2a with -Methylbenzylamine to Form Imine 9

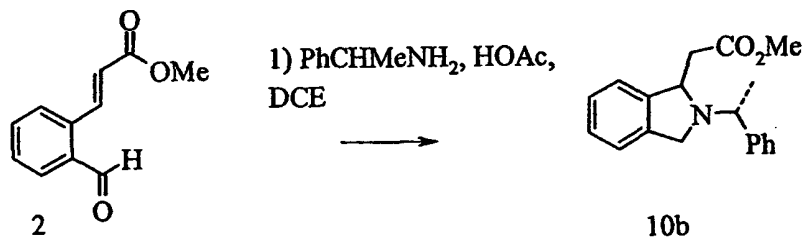


2-carboxaldehyde-methyl-cinnamate 2a (0.897 g, 4.72 mmol) was dissolved in MeOH (10 mL) at RT. R-(+)-phenethylamine (0.577 g, 4.76 mmol) was added and the solution was heated under reflux for 2 hours. HPLC In process control indicated that the imine formation was completed. The solvent was stripped on a rotary evaporator and the resulting oil was dried at RT under vacuum overnight. The Schiff base 9 was obtained almost quantitatively (1.412 g, 4.81 mmol).

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Preparation PP13

Michael Addition



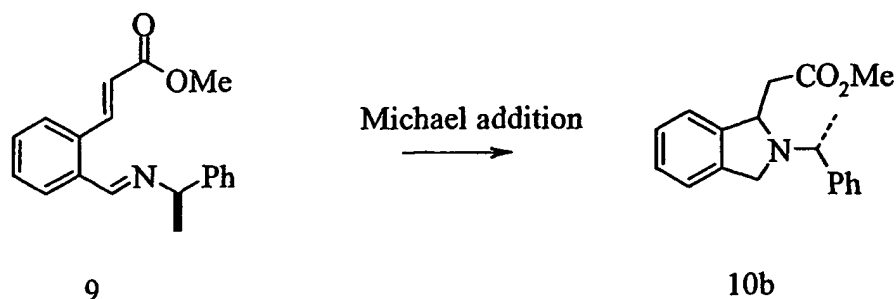
- 5 -Methyl benzylamine was applied as the auxiliary. As shown above, the one-pot reaction of aldehyde 2a and -Methyl benzylamine gave 90% of 10b with a ratio of 1.2:1.

Step-wise reduction, amination, and cyclization:

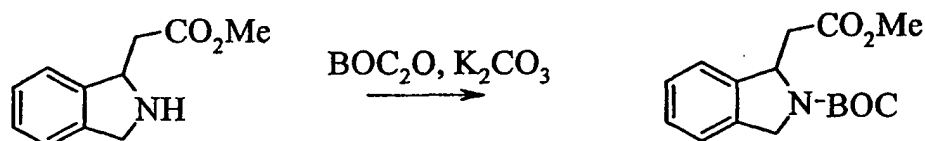
- Condensation of aldehyde 2a with -methylbenzylamine in acetonitrile or toluene afforded imine 9 in excellent yield. Reduction of the imine was initially carried out at RT with NaCNBH₃/HOAc. As a result, a poor ee ratio (1.2:1) was obtained, similarly to the previous described one-pot procedure. But when the reaction was carried out with NaBH₄/TFA at RT, the ratio was elevated to 2:1. By lowering the reaction temperature to -78 °C, the ratio was increased to 5-6:1.

Conditions	Ratio
NaCNBH ₃ , HOAc, rt	1.2:1
NaBH ₄ , TFA, rt	2:1
NaBH ₄ , TFA, -78°C	5-6:1

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Preparation PP14Cyclization of *t*-Butyl carbamate (11a)

The *N*-Boc isoindoline methyl ester 12 was originally synthesized from 11a via deprotection of Boc with TFA, followed by basic workup, and protection with a Boc group. This procedure has been greatly improved by a one-step procedure.

Preparation PP15

In a 3 L 3-neck round bottom flask equipped with a nitrogen inlet, thermocouple and mechanical stirrer, a solution of 160 g (1.15 moles) of K_2CO_3 in 180 mL of water was stirred at rt. Solid BOC anhydride 120 g (0.55 moles) was added in one portion forming a semi-solution. To the reaction mixture, a solution of the crude amino ester starting material, 87 g (0.46 moles) in 120 mL of THF was added slowly at such a rate to keep the internal temperature below 35°C. A mild effervescence was observed. The reaction mixture was stirred for 18 hours at rt. Analysis of a reaction aliquot via NMR (DMSO-d_6) indicates the desired product. The reaction was diluted with brine and the product extracted with EtOAc. The organic layer was dried over Na_2SO_4 , filtered, and concentrated to yield a dark oil, 150.1 g, >100% yield. The crude material was taken on to the next step.

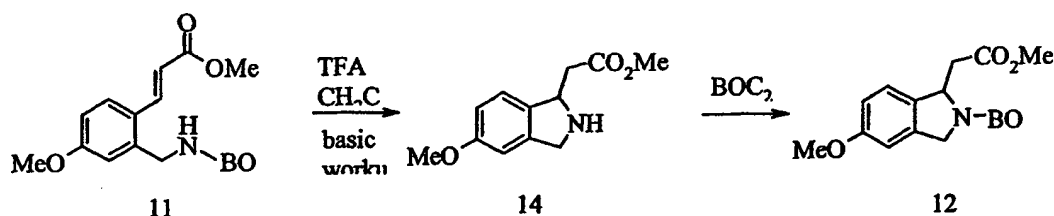
-80-

Preparation PP16

In a 3 L 3-neck round bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condenser, a solution of 150 g (approx. 0.46 moles) of crude N-BOC ester starting material in 750 mL of methanol was stirred at rt. To the solution, 750 mL of water was added and the cloudy mixture was stirred vigorously. Solid LiOH 25 g (1.03 moles) was added in small portions at such a rate to maintain the internal temperature below 45 °C. Upon completion of addition, the reaction was stirred overnight at rt becoming a dark green color. After 18 hours the reaction was concentrated to yield a thick semisolid. The crude product was dissolved in EtOAc and washed with 1 N HCl quickly, followed by two brine washes. The organic layer was dried with Na₂SO₄, filtered and concentrated to yield 81 g of a dark green solid. The aqueous layers were combined and back extracted with methylene chloride, dried over Na₂SO₄, filtered, and concentrated to yield 6 g of a dark green solid. Both solids were combined to yield 87 g of desired product confirmed via NMR (DMSO₆).

Preparation PP17

Synthesis of 14b



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Dissolved the N-boc compound 11b (200 mg, 0.62 mmol) in CH₂Cl₂ (1.0 mL). Cooled the clear light yellow solution to 0°C. Added slowly TFA (~710 mg, 10 eq, ~500 µL) via a syringe. Removed the cooling bath and stirred the clear light brown solution at RT overnight. TLC (3:1 Hex / EtOAc, UV) confirmed a complete reaction. Removed the TFA on a rotavapor. Added EtOAc and concentrated again (twice). The crude residue was partitioned between EtOAc (10-15 mL) and a sat. NaHCO₃ (10-15 mL). The

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aqueous was extracted with EtOAc (2x10 mL). The combined organic was dried over MgSO₄, filtered, and concentrated to yield a light brown wet solid (212 mg, 138 %). NMR (CD₃OD) confirmed the desired isoindoline 14b. This crude isoindoline was used in the next protection step without purification.

5

Preparation PP18

Synthesis of 12b

To a mixture of the isoindoline 14b (190 mg, 0.859 mmol), K₂CO₃ (189 mg, 1.5 eq) in a solvent 1:1 THF / H₂O (1.0 mL) at RT was added BOC₂O (210 mg, 1.1 eq). The reaction mixture was stirred at RT overnight. TLC (3:1 Hex / EtOAc, UV) confirmed a complete reaction. Diluted the mixture with EtOAc (15 mL), and washed with H₂O (1x20 mL). The aqueous was extracted with EtOAc (1x20 mL). The combined organic was washed with brine (1x20 mL), dried over MgSO₄, filtered, concentrated to yield a clear brown oil (340 mg, 123 %). This crude oil was purified on a prep TLC plate (2x1,000 micron, solvent 2:1.5:0.5 CHCl₃ / Hex / EtOAc) to yield 12b a clear yellow oil (190 mg, 69 %). ¹H and ¹³C NMR (CDCl₃) were obtained.

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Procedure PP19

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Synthesis of 12d (5-NO₂) by Boc-protection

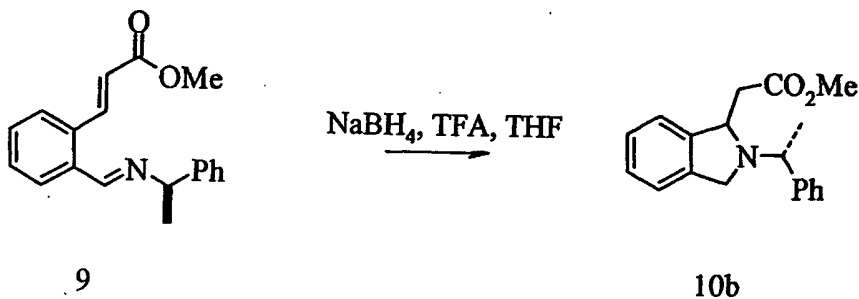
The procedure is same as that of 12b.

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Preparation PP20

Synthesis of 10b

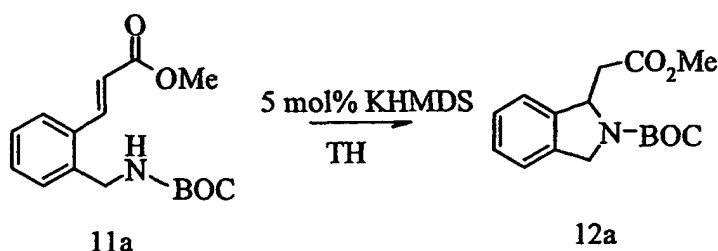


- 5 The imine 9 (1.412 g, 4.81 mmol) was dissolved in anhydrous THF (10 mL) at RT and TFA (5 mL) was added. The black solution was then cooled to -78°C (dry ice bath) and NaBH_4 (0.893 g, 23.6 mmol, 5 eq.) was added in 2 portions over 5 minutes. Then, the reaction mixture was post-agitated at -78°C for 3 hours and allowed to gently warm at RT overnight. Water (20 mL), cyclohexane (10 mL) and EtOH (20 mL) were
- 10 successively added and the organic layer was extracted and discarded. The aqueous layer was made basic with 5N NaOH (20 mL) and extracted two times with a 2:1 EtOAc/ PhCH_3 mixture (30 mL). The combined organic layers were dried over MgSO_4 , filtered and rinsed with EtOAc (10 mL). The filtrates were concentrated under reduced pressure and the residual oil was dried under vacuum overnight at RT to afford the target cyclized
- 15 isoindoline product 10b (1.273 g, 4.31 mmol) with 91.4% yield. HPLC % area indicated that the 2 diastereomers were produced in a 84:16 ratio (de 68%). ^1H NMR confirmed this result by integration of the methyl group of the phenethyl substituent.

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Preparation PP21

Cyclization of (11a)/Formation of (12a)



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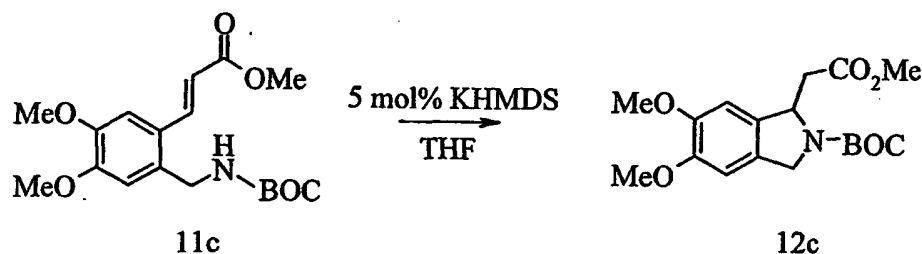
Dissolved the N-Boc methyl ester 11a (36.3 g, 0.125 mol) in THF (250 mL). Cooled the solution to 0°C. Added slowly a solution of potassium bis(trimethylsilyl)amide (1.24 g, 0.05 mol. Eq.) via a syringe under nitrogen atmosphere. The temperature was raised about 8 degrees during the addition. Removed the cooling bath and stirred the clear brown solution at room temperature for 30-45 min. TLC (3:1 Hex/EtOAc) confirmed a complete reaction. Poured the clear brown solution into a separation funnel containing about 100 mL of a saturated NH₄Cl and a few crushed ice. The layers were separated. The aqueous layer was extracted with EtOAc (2x50 mL). The combined organic was washed with brine (1x100 mL), dried over Na₂SO₄, filtered, concentrated on a Rotary evaporator to a clear yellow oil (37.3 g). This crude oil was purified on a flash column (600 g SiO₂), with a gradient solvent 6:1 Hex/EtOAc (2.1 L), 5:1 Hex/EtOAc (1.2 L), 4:1 Hex/EtOAc (1.5 L) to yield 12a as a clean yellow oil (34.5 g, 95 %).

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Preparation PP22

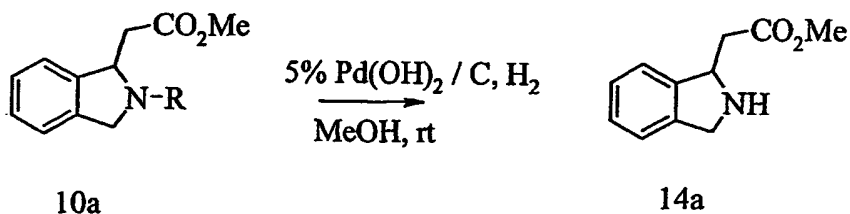
Cyclization of (11c). Formation of (12c)



- 5 To a solution of 11c (535 mg, 1.52 mmol) in THF (10 mL) was added KHMDS (0.5 M in toluene, 0.1 mL, 0.05 mmol, 2 mol%). The mixture was stirred at rt for 20 min, quenched with sat. NH_4Cl solution (20 mL), and diluted with EtOAc (20 mL). The organic layer was separated, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was filtered through a plug of silica gel (EtOAc/ CH_2Cl_2 1:10)
- 10 to give 530 mg (99%) of 12c as an off white solid.

Preparation PP23

Hydrogenolysis of 10a (R = Bn) to Form (14a)



15

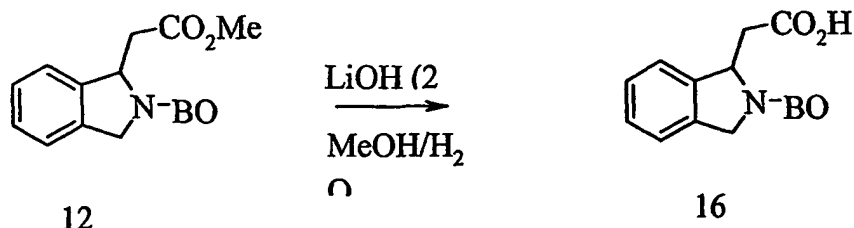
Deprotections:

- To a solution of crude 10a (15.3 g, 54.4 mmol) in MeOH (100 mL) was added $\text{Pd(OH)}_2/\text{C}$ (Pearlman's catalyst, 1.02 g, 6 mol%) in a par-shaker bottle. The suspension was shaken under 30 psi H_2 pressure overnight in the par-shaker, and filtered through a plug of celite. The filtrate was concentrated to provide 10.1 g of crude 14a as brown oil.
- 20 (The procedure is same for the methyl benzylamine isoindoline substrate 10b).

-85-

Preparation PP24

Hydrolysis of Isoindoline Methyl Ester (12a). Formation of Isoindolinecarboxylic Acid (16a)



In a typical reaction a mixture of the isoindoline ester 12a (92 mg, 0.316 mmol) in 1:1 MeOH/H₂O (2 ml) was treated with LiOH (15 mg, 2 eq) at RT overnight. Diluted the mixture with CH₂Cl₂ (5 ml) and water (5 ml). Adjusted the pH of the reaction mixture to 1-3 with a 10% NaHSO₄ solution. Separated the layers. The aqueous was extracted with CH₂Cl₂ (1 x 10 ml). The combined organic was dried over Na₂SO₄, filtered, concentrated to yield 16a as a pale yellow foam (76 mg, 87 %). NMR (CDCl₃) showed a clean desired acid product.

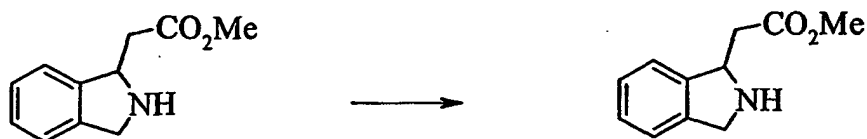
Note: 1. Reaction time must be more than 6 hours.

2. The crude foam can be purified by slurry in warm hexane and then filter to yield a tan solid.

3. Hydrolysis using KOH (2-5 eq) in 1:1 MeOH/H₂O overnight will give the same result.

Preparation PP25

Purification of Partially Resolved Isoindolinecarboxylic acid methyl ester



Resolution:

A solution of the crude material (97.62g) isoindolinecarboxylic acid methyl ester in CH₂Cl₂ (350 mL) was extracted with 1M HCl (400 mL, 200 mL). The combined aqueous portions were washed with CH₂Cl₂ (4 X 250 mL) and then made basic with K₂CO₃

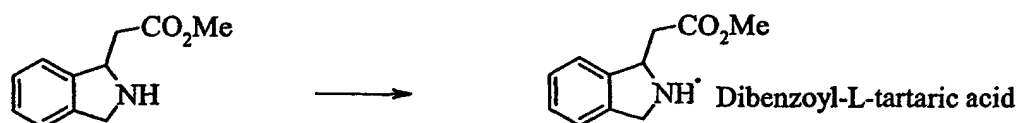
-86-

solution (85 g in 150 mL of water). The mixture was extracted with CH_2Cl_2 (6 X 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give partially resolved Isoindolinecarboxylic acid methyl ester as an oil (33.2 g). 60% ee by chiral CE.

5

Preparation PP26

Resolution of Partially Resolved Isoindolinecarboxylic acid methyl ester



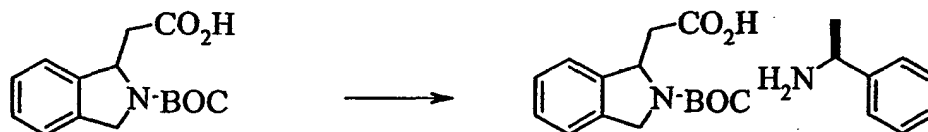
10

A solution of partially resolved isoindolinecarboxylic acid methyl ester (33.24 g, 0.174 mol) in EtOH (130 mL) was treated slowly with a solution of dibenzoyl-L-tartaric acid (56.06 g, 0.156 mol) in EtOH (200 mL). The solution was seeded with product and stirred at RT for 4 hours. Pure product was collected by filtration, washed with EtOH (30 mL) and dried to off-white crystals (60.49 g). 96.5% ee by chiral CE.

15

Preparation PP27

Resolution of N-BOC Isoindolinecarboxylic acid



20

A solution / slurry of racemic N-BOC Isoindolinecarboxylic acid (114.5 g, 0.413 mol) in EtOAc (1000 mL) was treated slowly with triethylamine (28.8 mL, 0.206 mol), followed by (S)-(-)- α -methylbenzylamine. The solution was seeded with product and stirred at RT overnight. Product was collected by filtration, washed with EtOAc (200 mL) and dried to a white powder (62.98 g). 97.6% ee by chiral CE.

25

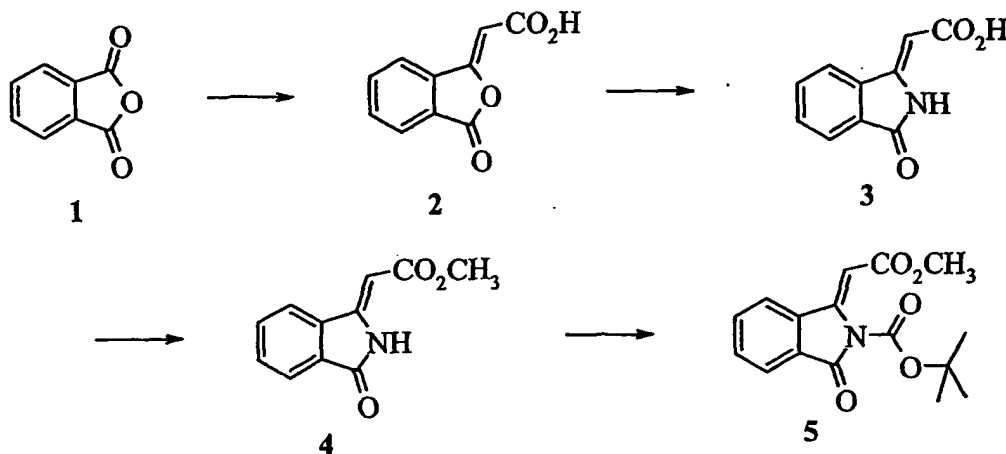
-87-

Preparation PP28

Part I. Synthesis of the Z-isomer (precursor of asymmetric hydrogenation)

Scheme P1

5



Asymmetric Hydrogenation Routes:

Z-isomer 5 was synthesized as outlined in Scheme P1. Compound 5 was shown to be a single isomer by HPLC and H-1 nmr. The double bond stereochemistry was derived from comparative NOE data using the purported E-isomer (Scheme P1). The best chiral induction was achieved using compound 8/Ferrotane/MeOH-THF. With regard to the conversion of 9 to 10, which would constitute a formal asymmetric synthesis of isoindolene 10, this has been achieved using Super hydride-BF₃.OEt₂. However, the product was a mixture of 10 and the corresponding de-BOC (deprotected) compound.

Preparation PP29

Compound 2 (Scheme P1)

Phthalic anhydride (751.5g, 5.014 mole), potassium acetate (498g, 5.014 mole) and acetic anhydride (1L) were stirred together under nitrogen. The mixture was slowly warmed to 145-150°C and stirred for 10 minutes, then at 140°C for 20 minutes. The mixture was allowed to slowly cool to 80°C over 1 hour. Three volumes of water were added causing precipitation of a solid. After filtration, the filtered solid was washed with warm water and pulled as dry as possible for 30 minutes. The solid was then washed with

-88-

ethanol and acetone respectively. If required further purification could be achieved by slurrying the solid in acetone, at room temperature, for 15 minutes, then filtration. Drying in vacuo at 50°C for 20 hours gave compound 2 as an off-white solid, 470g (48%) with an NMR purity of approx. 90%.

5

Preparation PP30

Compound 3 (Scheme P1)

Compound 2 (470g, 2.47 mole) was added to stirred aqueous ammonia (470 ml conc. NH₃ in 4.7L water). The resultant mixture was stirred at room temperature for 1 hour then filtered. The filtered solid was washed with water. The combined aqueous filtrate and washings were carefully acidified with 6M aq. HCl (2.35L). The precipitate was removed by filtration and dried in vacuo at 50°C to give compound 3 as a yellow solid, 259g (52%).

15

Preparation PP31

Compound 4 (Scheme P1)

Compound 3 (511g, 2.7 mole) was slurried in toluene (10 vol). Thionyl chloride (385g, 3.24 mole) was added over 10 minutes to the stirred mixture, which was then heated to reflux for 1.5 hours. H-1 NMR analysis indicated approx. 80% conversion to acid chloride). DMF (3.7ml) was added and the mixture refluxed an additional 3 hours. The resultant mixture was allowed to cool to 35°C and methanol (1.27L) added at such a rate that the reaction temperature was maintained at 30-35°C. The reaction mixture was kept at this temperature a further 15 minutes then concentrated in vacuo to give compound 4 as a brown solid, 536g (quantitative).

20
25

-89-

Preparation PP32

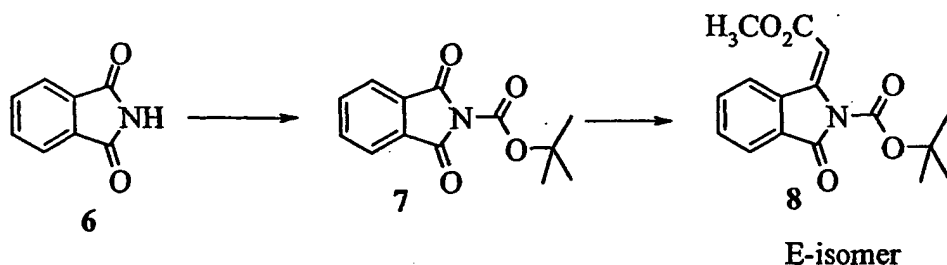
Compound 5 (Scheme P1)

Compound 4 (750g, 3.65 mole) was dissolved in acetonitrile (15L). The stirred mixture was cooled to 0-5°C and DMAP (624g, 5.11 mole) added in one portion. After 10 minutes BOC anhydride (1115g, 5.11 mole) was added in one portion: there was a slight exotherm accompanied by gas evolution. The mixture was stirred at room temperature for 5 hours, and then concentrated in vacuo. The residue was dissolved in EtOAc and washed with 10% aqueous citric acid, satd. aq. Na₂CO₃ and water respectively. After drying, concentration of the organics gave a thick syrup. This material was run through a plug of silica gel (1.5kg) eluting with 1:1 EtOAc-hexane. Compound 5 was isolated as a dark solid, 619g (55%). Careful chromatography on silica gel eluting with 20% EtOAc-hexane gave 5 as a fluffy white solid.

Preparation PP33

Part II. Synthesis of the E-isomer (Precursor of asymmetric hydrogenation)

Scheme P2



The E-isomer of Compound 8 (Scheme P2), was prepared as shown in Scheme P2.

-90-

Preparation PP33

Compound 7 (Scheme P2)

Compound 7 was prepared according to the procedure of Einhorn et al, *Synth. Commun.* 2001, 31(5), 741-748.

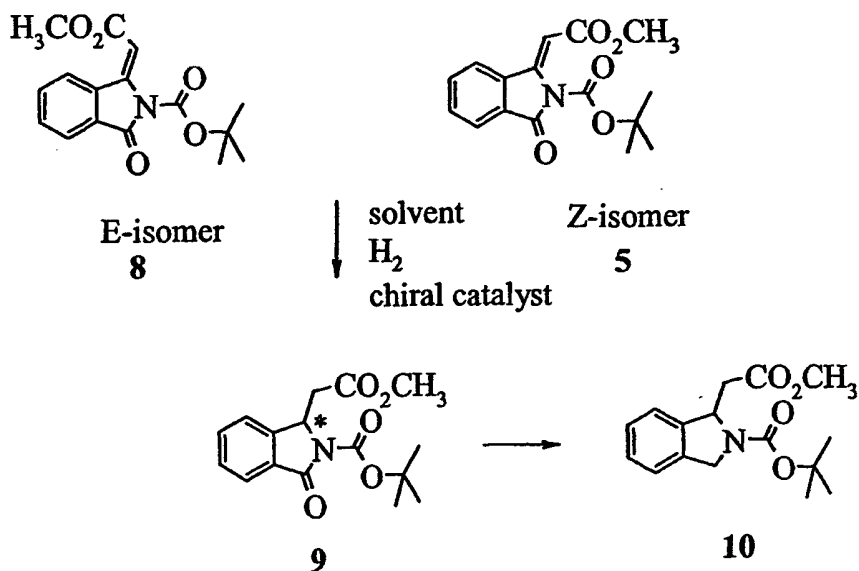
Preparation PP34

Compound 8 (Scheme P2)

Compound 7 (15.00g, 60.7 mmole) and methyl(triphenylphosphoranylidene) acetate (41.40g, 121.3 mmole) were slurried in toluene (150ml). The mixture was stirred at reflux and monitored for reaction of 7 by GC. After 1.5 hours the reaction appears complete by GC. After cooling to room temperature, the mixture was filtered. The solid on the filter was washed with toluene until colorless. The combined filtrate / washings were concentrated in vacuo to leave a tan solid. This material was coated on silica gel and chromatographed on silica gel (1kg) eluting with 10% EtOAc-hexane. Compound 8 was isolated as a white or pale yellow powder, 5.52g (30%).

Asymmetric hydrogenation:

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Scheme P3

-91-

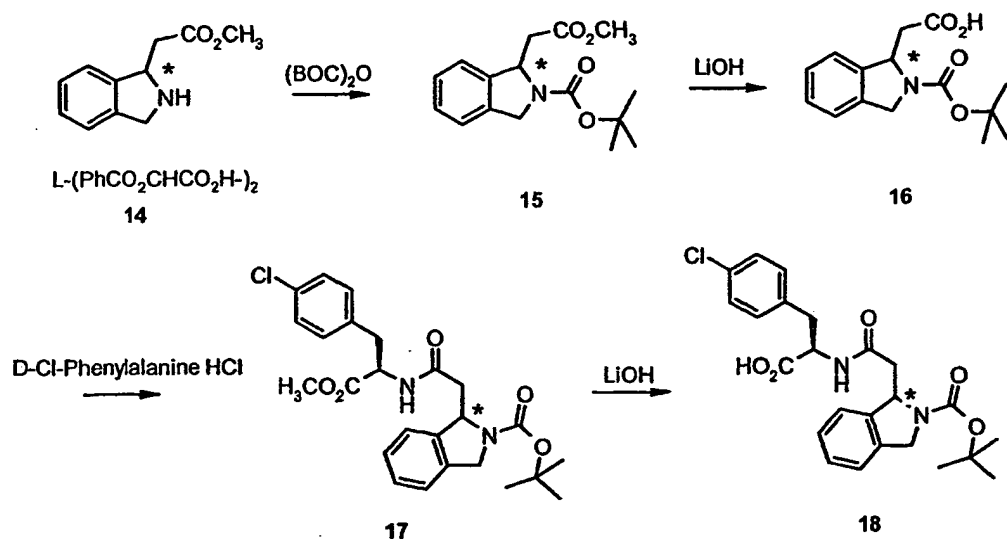
Preparation PP35

Screening of chiral hydrogenation conditions indicated that the best chiral induction was achieved using compound 8/Ferrotane/MeOH-THF. With regard to the conversion of 9 to 10, which would constitute a formal asymmetric synthesis of isoindolene 10, this has been achieved using Super hydride-BF₃.OEt₂. However, the product was a mixture of 10 and the corresponding de-BOC (deprotected) compound.

Coupling of chiral isoindoline with d-4-Chloro-Phenylalanine:

(Using tartrate salt)

10

Scheme P4Preparation PP36

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Compound 15 (Scheme P4)

Tartrate salt 14 (58.00g, 100.27 mmole) was slurried in water (580ml). Solid NaHCO₃ (25.27g, 300.8 mmole) was carefully added. BOC anhydride (22.98g, 105.28 mmole) was added in one portion and the progress of the reaction monitored by reverse phase HPLC. After 1 hour additional BOC anhydride (2.18g, 10.00 mmole) was added. The reaction was complete (by HPLC) after 3 hours. The mixture was extracted with EtOAc (2 x 250ml). The combined organic extracts were washed with water (250ml) and dried (MgSO₄). Filtration and concentration in vacuo gave 15 as a clear light brown oil

-92-

(31.33g) contaminated with a small amount of t-BuOH and BOC anhydride. This material was used directly in the next reaction.

Preparation PP37

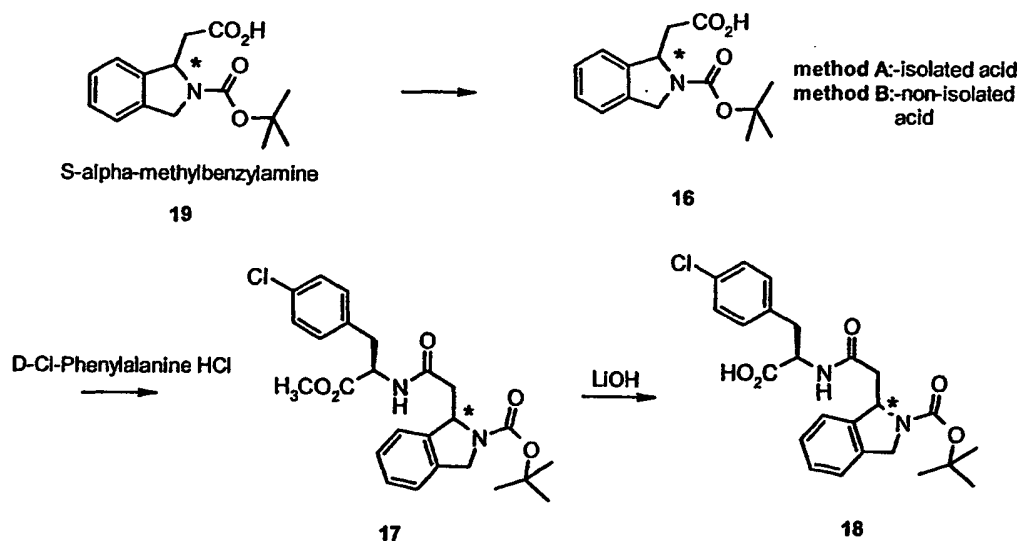
5

Compound 16 (Scheme P4)

Ester 15 (29.21g, 100.26 mmole) was dissolved in 3:1 THF-water (100ml). LiOH (6.00g, 250.65 mmole) was added in 1 portion to the stirred solution. After 17 hours, the mixture was stripped to dryness and the residue dissolved in water (500ml). EtOAc (250ml) was added and solid NaHSO₄ added to the stirred mixture until the pH=3. The organic layer was separated and the aqueous layer extracted with EtOAc (250ml). The combined EtOAc layers were dried (MgSO₄). Filtration and concentration in vacuo gave acid 16 as a light tan solid, 27.10g (97%).

15 (From alpha-methyl benzylamine salt):

Scheme P5



20

The chemistry used is shown in Scheme P5. Two protocols were used: method A used isolated 16, method B used a solution of 16 derived from resolved salt 19.

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Preparation PP38

Compound 17 (Scheme P5, method A)

5 Acid 16 (24.18g, 87.2 mmole) and D-chloro-phenylalanine hydrochloride (21.81g, 87.2 mmole) were dissolved in CH₂Cl₂ (100ml) and DMF (25ml). The mixture was stirred at ambient temperature. HOBT (13.55g, 100.3 mmole) and Hunig's base (45.6ml, 33.81g, 261.6 mmole) were added. HATU (38.13g, 100.3mmole) was added in 1 portion (there was a rapid exotherm to 50°C). The mixture was stirred for 90 minutes then diluted with EtOAc (750ml). The resulting mixture was washed with water, 5% KHSO₄, brine and satd. NaHCO₃ respectively, then dried. Filtration and concentration in vacuo gave
10 crude 17 as a brown foam. The product was purified by chromatography on silica gel (1kg) eluting with 1:1 EtOAc-hexane. Ester 17 was isolated as a tan powder, 38.85g (94%).

Preparation PP39

Compound 17 (Scheme P5, method B)

15 Resolved salt 19 (96.27g, 232.5 mmole) was partitioned between water (500ml) and CH₂Cl₂ (250ml) Solid KHSO₄ was added portion wise until pH=2.5. Separate the
20 organic layer and extract the aqueous layer with CH₂Cl₂ (150ml). The combined organic layers were dried (MgSO₄) then filtered. To this solution was added 4-chloro-D-phenylalanine (58.16g, 232.5 mmole), HOBT (34.57g, 255.8 mmole), Hunig's base (93.2ml, 69.13g, 534.9 mmole) and finally HATU (97.26g, 255.8 mmole). The resultant mixture was stirred at room temperature for 18.5 hours, and then poured onto a plug of
25 silica gel (1kg). This was washed with 1:1 EtOAc-hexane until no more product elutes. Ester 17 was isolated as a pink foam, 101.79g (93%): contains about 1% unreacted 16.

-94-

Preparation PP40

Compound 18 (Scheme P5)

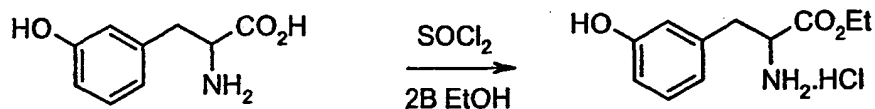
Ester 17 (38.64g, 81.7 mmole) was dissolved in 3:1 THF-water (200ml). LiOH
5 (2.15g, 89.9 mmole) was added to the mixture, which was stirred at room temperature for
2 hours. The solvent was then removed in vacuo and the residual solid taken up in water
(600ml). This was extracted with MTBE (250ml). The aqueous layer was separated and
stirred with EtOAc (250ml), and solid KHSO₄ was added portion wise until pH=3. The
layers were separated and the aqueous extracted with EtOAc (250ml). The combined
10 organic layers were dried over MgSO₄. Filtration and concentration in vacuo gave acid
18 as a light pink foam, 38.41g (35.71g corrected for residual solvent, 95%).

Procedures for preparing isoquinoline carboxylate intermediates:

15

Preparation PP41

Step 1 Esterification:



20

In a 22 L 4-neck round bottom flask equipped with a reflux condenser,
thermocouple and nitrogen inlet, a slurry of 1000 g (5.4 moles) of m-tyrosine in 10 L of
2B-3 EtOH was cooled to 5 °C. To the slurry, 350 mL (12.4 moles) of thionyl chloride
were added dropwise via an addition funnel at such a rate to maintain the reaction
25 temperature below 20 °C. Upon completion of addition, the reaction was heated to reflux
temperature and stirred for 18 hrs. The reaction was concentrated to one-third the volume
and 8 L of MTBE were charged. The resulting thick slurry was stirred for 14 hrs in a
rotary evaporator at rt. The resulting solid was isolated on a filter pad and dried at 40 °C
for 48 hrs yielding 1288 g (95%). NMR (DMSO-d₆) indicated desired material.

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-95-

Preparation PP42

Step 2 Pictet-Spengler:

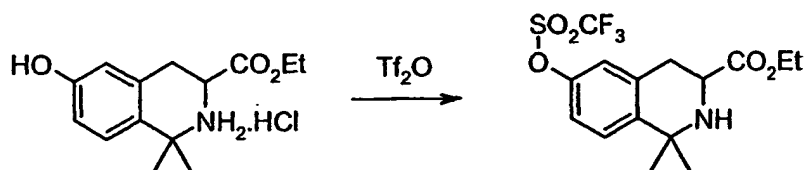


5 In a 22 L 4 neck round bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condenser placed on top of a Soxhlet extractor charged with 4°A sieves, a semi-solution of *m*-tyrosine ethyl ester hydrochloride 1288 g (5.26 moles) in 13 L of acetone was heated to reflux temperature. The condensate was filtered through
10 the sieves to remove water. The reaction was stirred vigorously at reflux for 48 hrs. An NMR sample in DMSO_d₆ indicated the absence of starting material. The reaction was cooled to rt and concentrated to yield an off-white solid, 1411 g (94%).

Preparation PP43

15

Step 3 Triflation:



In a 22 L 4 neck round bottom flask equipped with a reflux condenser, mechanical stirrer, nitrogen inlet, and a thermocouple, 1240 g (4.35 moles) of the starting material
20 salt in 12.4 L of methylene chloride was cooled to 4 °C. To the mixture, 1452 mL (10.4 moles) of triethylamine were added and stirred into solution. Triflic anhydride, 1472 mL (5.22 moles) was added dropwise to the reaction at such a rate to maintain the internal temperature below 10°C. The ice bath was removed and the reaction warmed to rt. and stirred for 18 hrs. The reaction was concentrated to a oil then dissolved in 4 L of EtOAc
25 and concentrated again to an oil in an effort to remove excess triflic anhydride. The crude residue was dissolved in 4 L of EtOAc and washed with water and saturated sodium bicarbonate solution. The organic layer was isolated and dried with sodium sulfate,

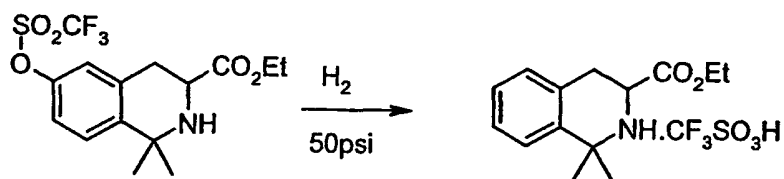
-96-

filtered and concentrated to yield 1720 g (>100%) of a crude dark oil which was used without further purification.

Preparation PP44

5

Step 4 Deoxygenation:



- 10 A solution of 1720 g (4.35 moles) of crude starting material in 14 L of acetone was charged to a 10 gallon stainless steel autoclave. To the solution, a slurry of 5% Pd/C in 1.2 L of toluene was added. The reaction mixture was evacuated and purged with H_2 gas at 50 psi two times. The reaction was stirred overnight at 50 °C with H_2 at 50 psi. A sample aliquot indicated no reaction had occurred. The mixture was filtered and
- 15 concentrated to a thick oil and resubjected to reaction conditions. After 18 hrs, NMR of a sample aliquot indicated absence of starting material. The reaction mixture was filtered and the filtrate concentrated to yield 1581 g of an off-white solid (95%).

Preparation PP45

20

Step 5 Hydrolysis/Salt Formation:



- 25 To a 2 L 3 neck round bottom flask equipped with a mechanical stirrer, thermocouple, and nitrogen inlet, a mixture of 700 g (1.83 moles) of the triflate salt starting material was charged. A solution of 427 g (1.83 moles) of the starting material free base in 13.3 L of THF was added followed by 700 mL of water. The semi-solution

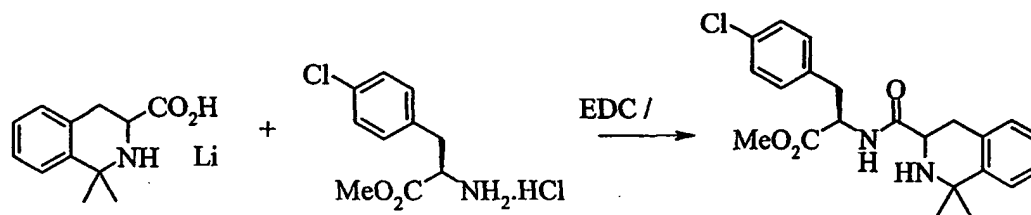
-97-

was stirred vigorously at rt. To the reaction flask, 43.7 g (1.83 moles) of solid LiOH were added in small portions at such a rate to maintain the internal temperature below 35 °C. The reaction was stirred for 18 hrs at rt and concentrated to yield a thick oil. THF (4 L) was added and the semi-solution was concentrated. This was repeated with toluene and the semi-solid was placed under house vacuum on the roto vap with stirring for 18 hrs. to yield 650 g of a crude solid. The solid was reslurried in EtOAc, filtered, isolated and dried to yield 525 g (68%) of the lithium salt as an off-white solid.

Preparation PP46

10

Step 6 Coupling:

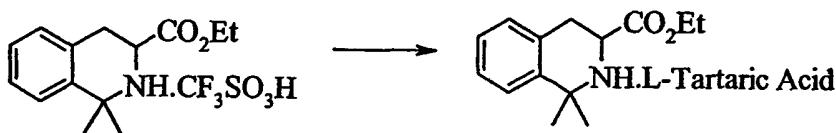


To a 12 L 4 neck flask equipped with a mechanical stirrer, water-cooled reflux condenser, thermocouple, and nitrogen inlet, a mixture of 400 g (1.62 mole) of the starting material free acid, 2 L of DMF, and 2 L of methylene chloride were stirred vigorously. Solid *d*-chloro-phenylalanine 446 g (1.78 moles) was added to the semi-solution followed by 20 g (0.162 moles) of DMAP. The resulting mixture was stirred for 15 minutes then solid EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) 390 g (2.03 moles) was added. The reaction mixture was heated to 80°C and stirred for 18 hours. Thin layer chromatography (1:1 EtOAc:Hex) indicated very little starting material present. The reaction was cooled to rt and concentrated to yield a thick oil. The crude oil was dissolved in EtOAc and washed with water, and brine. The solution was dried with sodium sulfate, filtered and concentrated to yield a thick oil, 426 g. The crude oil was chromatographed in several lots using a Waters Prep 500 chromatography apparatus. The eluent consisted of a gradient system, 5%-80% EtOAc in heptane at a flow rate of 240 ml/min over 38 minutes. The two diastereomers were separated and isolated to yield 119.04 g for the top spot and 111.3 g for the bottom spot. Conformation of both desired diastereomers was achieved via NMR (DMSO₆).

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Preparation PP47

Resolution



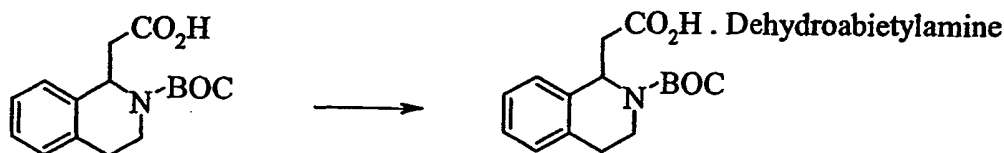
Resolution of tetrahydroisoquinolinecarboxylic acid ethyl ester to prepare 1-
5 tartaric acid salt:

Preparation of free-base: A racemic mixture of tetrahydroisoquinolinecarboxylic acid (7.43 g) in EtOAc (60 mL) was treated with saturated NaHCO₃ solution (60 mL) and saturated Na₂CO₃ solution (10 mL). The mixture was agitated and the layers were
10 separated. The organic phase was dried (Na₂SO₄) and concentrated to give the corresponding free-base as an oil (4.85 g).

Resolution: A mixture of the above free base (467 mg, 2.0 mmol), and L-tartaric acid (300 mg, 2.0 mmol) in acetone (4 mL) was stirred at RT overnight. The title L-tartaric acid salt was collected by filtration, washed with acetone (about 2 mL) and dried
15 to a white powder (367 mg). 100% ee by chiral CE.

Preparation PP48

20 2-{2-[(tert-butyl)oxycarbonyl]-1,2,3,4-tetrahydroisoquinolyl}acetic acid
dehydroabietylamine salt



Resolution of N-BOC tetrahydroisoquinolinecarboxylic acid to prepare:

Racemic 2-{2-[(tert-butyl)oxycarbonyl]-1,2,3,4-tetrahydroisoquinolyl}acetic acid
25 (30.15 g, 103.5 mmol) was dissolved in *i*-PA (300 mL). Dehydroabietylamine (22.11 g, 52.7 mmol of a 68 weight % mixture) was added to the solution, which was then agitated on a multi-arm shaker for 63 h. The resultant thick paste was filtered and rinsed with *i*-

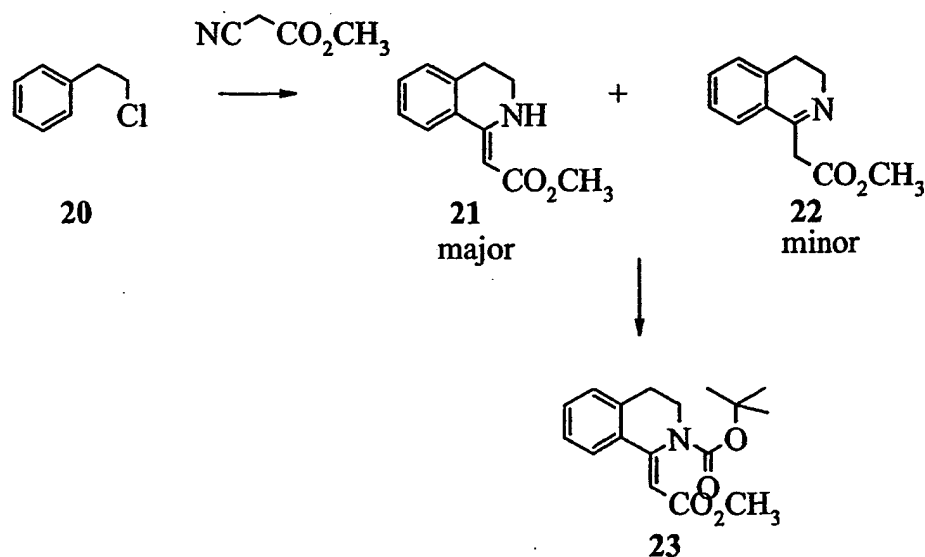
-99-

PA (50 mL, 25 mL). Dried in a 50 °C vacuum oven to obtain a white solid (27.73 g, 52 % ee by chiral CE analysis). The product was reslurried in *i*-PA (266 mL) and agitated on a multi-arm shaker for 23.5 h. Filtered the thick slurry and rinsed with cold *i*-PA (50 mL, 30 mL). Dried the cake in a 50 °C vacuum oven and obtained the product as a white solid (23.63 g, 40 % yield, 94 % ee by chiral CE analysis).

Preparation PP49

Scheme P6

10



Asymmetric Hydrogenation:

Enamine 21 (Scheme P6) was prepared as a substrate for asymmetric hydrogenation screening studies. It is formed as an approx. 10:1 mixture with imine 22. The enamine (21) may be NH-protected i.e. by a Boc protecting group. The resulting compound 23 may be subjected to asymmetric hydrogenation to afford the acetic acid or methylacetate substituted isoquinoline, which may be processed into a compound of formula I as demonstrated previously.

20

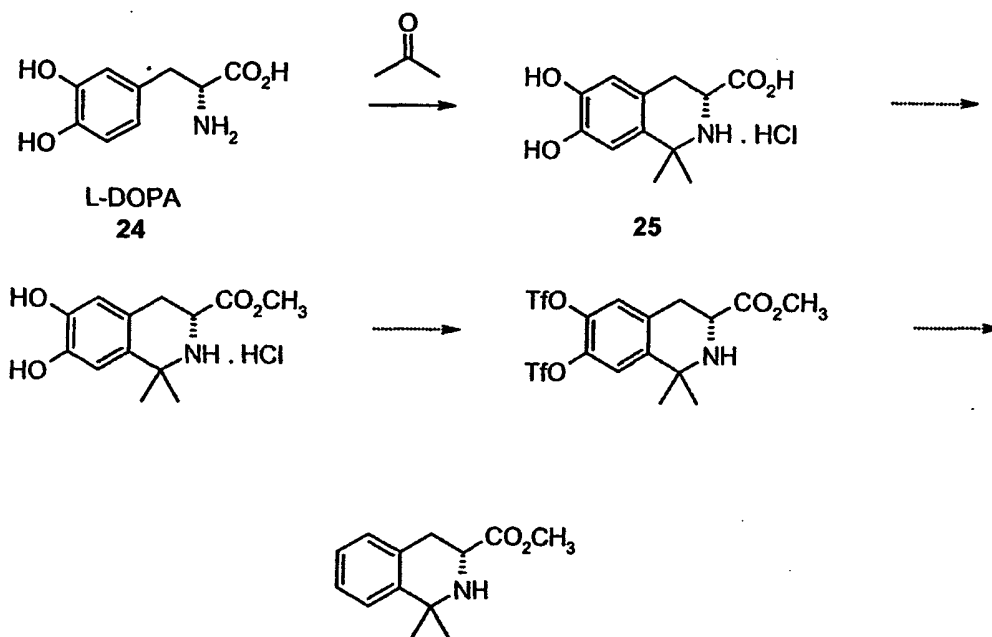
-100-

Preparation PP50

Compound 21 (Scheme P6)

Prepared as published W Sobotka et al, *J. Org. Chem.*, 1965, 30, 3667.Synthesis of Gem-dimethyl TIC

5

Scheme P7

10

Preparation PP51

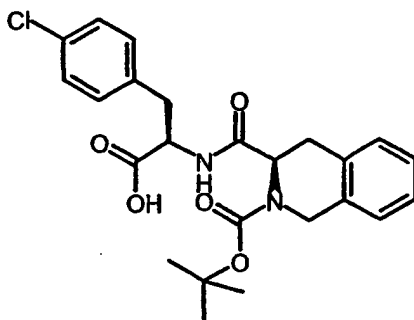
The chiral synthesis of gem-dimethyl TIC using L-Dopa as the starting material instead of tyrosine was successfully demonstrated up to the Pictet-Spengler reaction with L-DOPA and acetone. The product is a mixture of starting material 24 and product 25 (major component). The product was isolated by using common isolation procedures. An alternative isolation method is to react the mixture (24 and 25) with BOC anhydride wherein the less hindered N-H in 24 leads to preferential BOC protection of 24, allowing for ready separation of 25. Chemistry for the rest of the sequence has been demonstrated herein i.e. deoxygenation reaction, etc.

20

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Preparation BC1

3-[2-(4-Chloro-phenyl)-1-methoxycarbonyl-ethylcarbamoyl]-3,4-dihydro-1H-
isoquinoline-2-carboxylic acid tert-butyl ester



5

Preparation of Novel "B-C" Pieces:

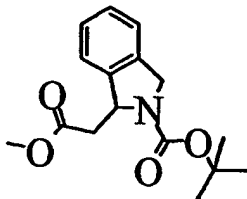
A. To a 0°C solution of 4-Chloro-D-Phe methyl ester (23.8 g, 111.0 mmol), Boc protected D-Tic (30.8 g, 111.0 mmol) and 4-DMAP (75 mg, 0.61 mmol) in 200 mL of DCM was added EDC (30.8 g, 111.0 mmol) and the mixture stirred for 20 minutes. The ice bath was removed and the mixture stirred at room temperature for 4 h. After washing with water (4 x 200 mL), the combined aqueous portions were back extracted with DCM (2 x 200 mL). The combined organic portions were washed with brine, dried (MgSO₄), and concentrated to dryness. The desired product was purified by flash chromatography (SiO₂, eluting with 35% EtOAc in Hexanes) affording 43.0 g (83%) of the ester. EIS MS
10 473 [M+1].
15

B. To the above-formed ester (43.0 g, 91.0 mmol), in MeOH (170 mL) at 0°C, was added 1N NaOH (227.0 mL, 227.0 mmol), dropwise. After 20 minutes the ice bath was removed and the mixture stirred at room temperature for 3 h. The mixture was
20 concentrated to dryness, and the resulting residue suspended in 200 mL of water. The aqueous layer was made acidic (pH 1) with 5 N hydrochloric acid and extracted with EtOAc (4 x 200 mL). The combined organics were dried (MgSO₄), filtered, and concentrated to dryness, affording 39.0 g (93%) of the title compound. EIS-MS 459 [M+1].
25

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Preparation C1

1-Methoxycarbonylmethyl-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester



A. (2-Bromo-benzyl)-carbamic acid tert-butyl ester:

5 To 2-bromobenzylamine hydrochloride (125.0 g, 561.8 mmol), in THF/water (1:1, 300 mL), was added potassium carbonate (170.7 g, 1236.0 mmol) and di-*tert*-butyl dicarbonate (134.9 g, 618.0 mmol), in four portions over 20 minutes. The mixture was stirred at room temperature for 16 h and diluted with 300 mL of EtOAc and 300 mL of water. The organic portion was separated and the aqueous portion was extracted with
10 EtOAc (3 x 200 mL). The combined EtOAc portions were washed with 250 mL of 10% aqueous sodium bisulfate, dried (MgSO₄), and concentrated to dryness to afford 161.0 g of the title compound.

B. 3-[2-(*tert*-Butoxycarbonylamino-methyl)-phenyl]-acrylic acid methyl ester:

15 To the product from part A (161.0 g, 561.8 mmol), in DMF (800 mL), was added methyl acrylate (58.0 g, 674.2 mmol), TEA (170.5 g, 1685.4 mmol), and dichlorobis(triphenylphosphine)palladium(II) (7.9 g, 11.2 mmol) and the mixture was heated at 80°C for 32 h. The mixture was cooled, diluted with 1000 mL of EtOAc and washed with 10% aqueous sodium bisulfate. The aqueous portion was extracted three
20 times with EtOAc and the combined organics were dried (Na₂SO₄) and concentrated to dryness. The residue was dissolved in a small amount of DCM and filtered through 7 in. of silica gel in a 2 L sintered glass funnel eluting with 25% EtOAc/hexanes. The eluent was concentrated to dryness and recrystallized from EtOAc/hexanes to afford 116.9 g (71%) of the title compound.

25

C. To a 0°C solution of the material from Part B (116.9 g, 401.2 mmol) in 800 mL of DCM was added 200 mL of TFA dropwise over 15 min. After removing the cooling bath, the mixture was stirred for 2.5 h and concentrated to dryness. The residue was

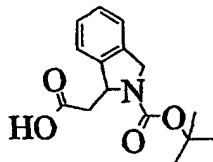
-103-

dissolved in 500 mL of DCM and saturated aqueous sodium bicarbonate was slowly added until the mixture was slightly basic. The organic portion was separated and the aqueous portion was extracted two times with DCM. The combined organic portions were dried (Na_2SO_4) and concentrated to dryness. The residue was dissolved in 800 mL of DCM and to the mixture was added DIPEA (57.0 g, 441.4 mmol) and di-*tert*-butyl dicarbonate (96.3 g, 441.4 mmol) in five portions over 45 minutes and the mixture stirred at room temperature for 16 h. The mixture was washed with 10% aqueous sodium bisulfate, the organic portion was separated and the aqueous portion extracted two times with DCM. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in a small amount of DCM and filtered through 7 in. of silica gel in a 2 L sintered glass funnel eluting with 25% EtOAc/hexanes. The eluent was concentrated to dryness and the enantiomers separated by chiral chromatography (Chiralcel OD). The first eluting isomer was labeled isomer #1 and the second eluting isomer #2; affording 52.6 g (45%) of the title compound (isomer 2).

EIS-MS 292 $[\text{M}+1]$.

Preparation C2

1-Carboxymethyl-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

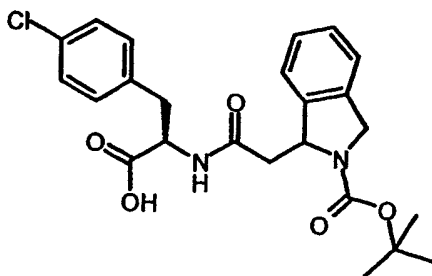


To the product from Preparation C1 (52.6 g, 180.5 mmol), in MeOH (500 mL), was added 1 *N* NaOH (199 mL, 199.0 mmol). The mixture was stirred at room temperature for 48 h and then concentrated to dryness. The resulting residue was dissolved in water (300 mL) and extracted with diethyl ether (2x). The aqueous portion was acidified to pH 2 with 10% aqueous sodium bisulfate and extracted with EtOAc. The combined organic extracts were dried (MgSO_4) and concentrated to dryness. Yield: 49.8 g, 99%. EIS-MS 276 $[\text{M}-1]$.

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Preparation BC2

1-[[1-Carboxy-2-(4-chloro-phenyl)-ethylcarbamoyl]-methyl]-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester



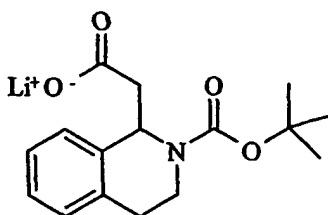
5 A. To a suspension of 4-Cl-D-Phe methyl ester hydrochloride (40.4 g, 161.5 mmol), in DCM (250 mL), was added saturated aqueous sodium bicarbonate (250 mL) and the mixture stirred at room temperature for 1 h. The organic portion was separated and the aqueous portion was extracted with DCM (2x). The combined organic portions were dried (Na_2SO_4) and concentrated to dryness. To the free amine, in DCM (400 mL) at
10 0°C , was added example C2 (isomer 2, 44.8 g, 161.5 mmol), EDC (31.0 g, 161.5 mmol) and 4-DMAP (2.0 g, 16.1 mmol). The reaction mixture was stirred at 0°C for 30 minutes whereupon the cooling bath was removed and the reaction mixture was stirred for another 5 h at room temperature. The mixture was then washed with saturated aqueous sodium bicarbonate (200 mL), 10% aqueous sodium bisulfate (200 mL), dried (Na_2SO_4), and the
15 organic phase was concentrated to dryness to afford 76.4 g (100%) of the ester. EIS-MS 471 [M-1].

B. To the ester from Part A (76.4 g, 161.5 mmol), in MeOH (760 mL), was added 1 N NaOH (242.0 mL, 242.0 mmol) and the mixture heated at 50°C for 4 h. then stirred for
20 another 16 h at room temperature. After concentrating to dryness, the resulting residue was taken up in 500 mL of water and washed with diethyl ether (2x). The aqueous portion was acidified to pH 2 with 10% aqueous sodium bisulfate and extracted with EtOAc (4 x 200 mL). The combined organic extracts were dried (MgSO_4) and concentrated to dryness. The resulting solid was suspended in hexanes, filtered, and dried
25 to afford 67.7 g (91%) of the title compound.
EIS-MS 457 [M-1].

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Preparation C3

1-Carboxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, lithium salt



5 A. (1,2,3,4-Tetrahydro-isoquinolin-1-yl)-acetic acid methyl ester:

To Boc-tetrahydroisoquinoline-1-acetic acid (100.4 g, 520.0 mmol), in MeOH (200 mL), was added 400mL of 2.3 M HCl in methanol. The mixture was stirred overnight and then concentrated to dryness. The resulting residue was dissolved in EtOAc, washed with saturated sodium bicarbonate, brine, dried (Na₂SO₄), and concentrated to dryness;

10 affording 109.5g (100%) of the ester.

EIS-MS 206 [M+1].

B. 1-Methoxycarbonylmethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester:

15

To a 0°C solution of material from part A (50.5g, 240.0 mmol), in THF (250 mL), was added di-*tert*-butyl dicarbonate (59.3 g, 270.0 mmol), in THF (50 mL), dropwise. After stirring 45 minutes, the mixture was concentrated to dryness. The resulting residue was dissolved in EtOAc, washed with saturated sodium bicarbonate, brine, dried

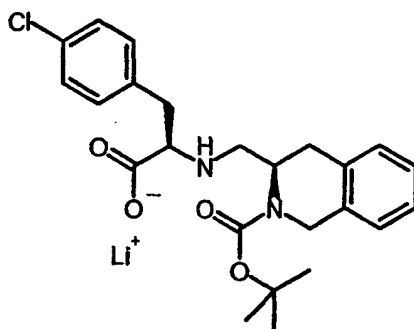
20 (Na₂SO₄), and concentrated to dryness. Chiral chromatography (Chiracel OD) of the residue afforded both enantiomers, with the first eluting isomer labeled isomer 1 and the second isomer 2. EIS-MS 306 [M+1].

C. To a solution of material from part B (10.2g, 33.4 mmol), in dioxane (220 mL),
25 was added a solution of lithium hydroxide monohydrate (1.67 g, 39.8 mmol), in water (110 mL), portionwise so as to maintain a temperature below 30°C. The mixture was stirred for 16 h and then concentrated to dryness; affording 11.2g of the lithium salt.
EIS-MS 292 [M+1].

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Preparation BC3

Lithium 2-[(2-tert-butoxycarbonyl-1,2,3,4-tetrahydro-isoquinolin-3-ylmethyl)-amino]-3-(4-chloro-phenyl)-propionate



5

A. 3-(Methoxy-methyl-carbamoyl)-3,4-dihydro-1H isoquinoline-2-carboxylic acid tert-butyl ester:

To Boc-D-1,2,3,4-tetrahydroisoquinoline carboxylic acid (14.9 g, 53.7mmol), in THF (500 mL), was added *N,O*-dimethylhydroxylamine hydrochloride (5.24 g, 53.7mmol), EDC (11.3g, 59.1mmol), HOBT (7.98g, 59.1mmol) and DIPEA (9.83ml, 56.4mmol). The mixture was stirred for 16 h, at room temperature and under nitrogen and then concentrated to dryness. The resulting residue was taken up in EtOAc, washed with 1M HCl, saturated sodium bicarbonate, brine, and dried (Na₂SO₄). After concentrating to dryness, the resulting residue was purified by flash chromatography (SiO₂, eluting with 1:1 EtOAc/hexane) to give 12.3g (71%) of the ester. EIS-MS 321 [M+1].

15

B. 3-Formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester:

To a 0°C solution of material from part A (1.28 g, 4.00mmol) in THF (30 mL), was slowly added 1.0 M LAH (in THF, 5.1ml, 5.1 mmol). The reaction mixture was stirred at 0°C for another 15 minutes. To the mixture was slowly added 20 mL of 5% aqueous potassium hydrogensulfate and the mixture extracted with Et₂O (2x). The combined organic portions were washed with 1M hydrochloric acid, saturated sodium bicarbonate, brine, dried (Na₂SO₄), and concentrated to dryness; affording 0.78 g (75%) of the title compound. EIS-MS 262 [M+1].

25

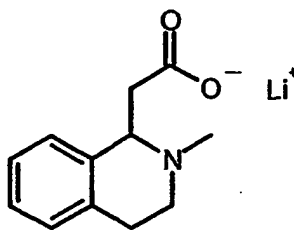
-107-

C. 3-{{2-(4-Chloro-phenyl)-1-methoxycarbonyl-ethylamino}-methyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester:

To a 0°C solution of 4-Cl-D-Phe methyl ester (6.27 g, 25.1 mmol) and sodium acetate (8.23g, 100.0mmol), in 850ml dry MeOH, was added material from part B (9.8g, 37.6mmol), in 50ml MeOH. The mixture was stirred for 15 minutes and then sodium cyanoborohydride (2.37g, 37.6mmol) added. The cooling bath was removed and the reaction stirred for 16 h at room temperature. The mixture was concentrated to dryness and the resulting residue taken up in water and 1ml of 1M HCl. The mixture was extracted with EtOAc and the organics washed with saturated sodium bicarbonate, brine, dried (Na₂SO₄), and concentrated to dryness. The resulting residue was purified by flash chromatography (SiO₂, eluting with 2:1 hexane/EtOAc) affording 8.62g (75%) of the title compound. EIS-MS 459 [M+1].

D. To a 12°C solution of material from part C (1.11g, 2.42mmol), in dioxane (15ml), was added a solution of lithium hydroxide (0.10 g, 2.42mmol), in water (7.5 mL). The mixture was stirred for 16 h and then concentrated to dryness; affording 1.08g (100%) of the title compound.
EIS-MS 445 [M+1].

Preparation C4



A. (1,2,3,4-Tetrahydro-isoquinolin-1-yl)-acetic acid methyl ester:

To the product from Preparation C3, part B (9.98g, 32.7 mmol) was added 500 mL of cold 4M HCl in dioxane. After one hour, the mixture was concentrated to dryness. The resulting residue was dissolved in EtOAc, the organics washed with saturated sodium

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bicarbonate, brine, dried (Na_2SO_4), and concentrated to dryness; affording 6.9 g (100%) of the amine. EIS-MS 206 [M+1].

B. (2-Methyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-acetic acid methyl ester:

5

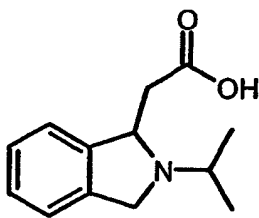
To the product from part A (6.71 g, 32.0 mmol), in dichloroethane (175 mL), was added 37% aqueous formaldehyde (22.6 mL, 300 mmol). After 10 minutes, sodium triacetoxyborohydride (31.2 g, 147.0 mmol) was added in 2-3 g portions, with cooling maintain so as to maintain ambient temperature. Upon completion of addition, the mixture was stirred for 16 h at room temperature. DCM and water was then added and the mixture adjusted to pH 9-10 with 5N NaOH. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to dryness. The resulting residue was purified by flash chromatography (SiO_2 , eluting with DCM/2N ammonia in methanol, 95:5); affording 6.9 g (96%) of the title compound. EIS-MS 220 [M+1].

15

C. To part B (4.45 g, 18.9 mmol), in dioxane (120 mL), was added lithium hydroxide monohydrate (1.02 g, 22.7 mmol), in water (65 mL) portion-wise; thereby keeping the temperature below 30°C . After 16 h the mixture was concentrated to dryness; affording 8.12 g of the title compound. EIS-MS 206 [M+1].

20

Preparation C5



A. (2,3-dihydro-1H-isoindol-1-yl)-acetic acid methyl ester:

25

To the product from Preparation C1 (11.75 g, 40.41 mmol), in DCM (50 mL), was added TFA (50 mL) dropwise. After 2 hr, the solution was concentrated to dryness and the resulting residue partitioned with saturated aqueous sodium bicarbonate (200 mL) and EtOAc (300 mL). The organic portion was separated and the aqueous layer was

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extracted with DCM (4 x 500 mL). The combined DCM extracts were combined, dried (Na_2SO_4), and concentrated to dryness to afford 3.97 g (51%) of the title compound.

B. (2-Isopropyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid methyl ester:

5

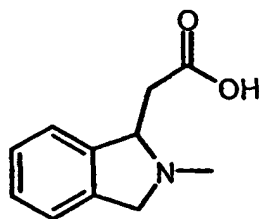
To the product from part A (0.50 g, 2.61 mmol), in dichloroethane (46 mL), was added acetone (1.76 mL, 24.01 mmol) and sodium triacetoxyborohydride (2.48 g., 11.74 mmol). After 6 h, the mixture was diluted with 1.0N NaOH (100 mL), the organic portion was separated and the aqueous layer extracted with DCM (3 x 100 mL). The combined DCM extracts were combined, dried (MgSO_4), and concentrated to dryness to afford 0.60 g (99%) of the title compound. EIS-MS 235 [M+1].

C. To the product from part B (0.53 g., 2.30 mmol), in MeOH (5.1 mL), was added 1.0N NaOH (2.53 mL, 2.53 mmol). After two days, the solution was concentrated to dryness. The resulting residue was diluted with 1.0N HCl and water then loaded onto a strong cation exchange resin. The resin was washed with water, THF / water (1:1), water, and the product eluted from the resin with pyridine/water (1:9). The eluent was concentrated to dryness to afford 0.43 g (85%) of the title compound. EIS-MS 220 [M+1].

20

Preparation C6

(2-Methyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid



25

A. (2-Methyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid methyl ester:

The product from Preparation C1 (0.50 g, 2.61 mmol) with the Boc-carbamate removed as described in step A of preparation C5, was dissolved in dichloroethane (46

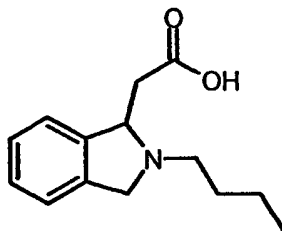
-110-

mL). This was followed by addition of 37% aqueous formaldehyde solution (1.80 mL, 24.01 mmol) and sodium triacetoxyborohydride (2.48 g., 11.74 mmol) with stirring. After 3 days, the mixture was diluted with 1.0N NaOH (100 mL). The organic portion was separated and the aqueous layer extracted with DCM (3 x 100 mL). The combined
5 DCM extracts were dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by flash chromatography (SiO_2 , eluting with 100% EtOAc); affording 0.43 g (79%) of the alkylated isoindole. EIS-MS 206 [M+1].

B. To the product from part A (0.34 g., 1.66 mmol), in MeOH (3.7 mL), was added
10 1.0N NaOH (1.82 mL, 1.82 mmol). After 2 days, the solution was concentrated to dryness. The resulting residue was diluted with 1.0N HCl and water then loaded onto a strong cation exchange resin. The resin was washed with water, THF / water (1:1), water, and the product eluted from the resin with pyridine/water (1:9). The eluent was concentrated to dryness to afford 0.31 g (98%) of the title compound. EIS-MS 192
15 [M+1].

Preparation C7

(2-Butyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid



20 A. (2-Butyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid methyl ester.

The product from Preparation C1 (0.50 g, 2.61 mmol), with the Boc carbamate (boc group) removed as described in Step A of Preparation C5 was dissolved in dichloroethane (46 mL) followed by addition of butyraldehyde (2.16 mL, 24.01 mmol)
25 and sodium triacetoxyborohydride (2.48 g., 11.74 mmol). After 3 days, the mixture was diluted with 1.0N NaOH (100 mL). The organic portion was separated and the aqueous layer extracted with DCM (3 x 75 mL). The combined DCM layers were dried (Na_2SO_4)

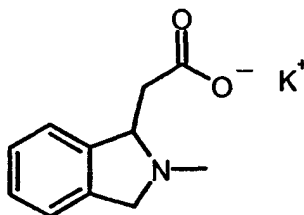
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and concentrated to dryness. The resulting residue was purified by flash chromatography (SiO₂, eluting with 1:3, EtOAc/hexanes); affording 0.51 g (77%) of the alkylated isoindole. EIS-MS 249 [M+1].

- 5 B. To the product from part A (0.47 g, 1.89 mmol) in MeOH (4.2 mL) was added 1.0N NaOH (2.08 mL, 2.08 mmol). After 2 days, the solution was concentrated to dryness. The residue was diluted with 1.0N HCl and water then loaded onto a strong cation exchange resin. The resin was washed with water, THF/water (1:1), water, and the product eluted from the resin with pyridine/water (1:9). The eluent was concentrated to
10 dryness to afford 0.28 g (64%) of the title compound. EIS-MS 234 [M+1].

Preparation C8

Potassium (2-methyl-2,3-dihydro-1H-isoindol-1-yl)-acetate



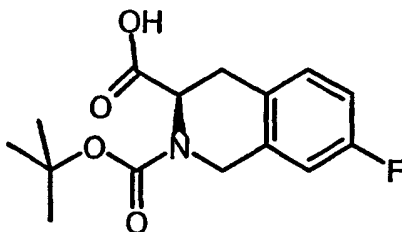
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- To Preparation C6, part A (2.65 gm, 12.9 mmol), in THF (27 mL) was added potassium trimethylsilanolate (1.66 gm, 12.9 mmol) and the reaction stirred for two days. After concentrating to dryness the resulting thick solid was triturated with diethyl ether,
20 filtered, washed with diethyl ether, and dried at room temperature to afford 2.73 g (92%) of the title compound. EIS-MS 192 [M+1].

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Preparation C9

7-Fluoro-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester



5 A. Amino-3-(4-fluoro-phenyl)-propionic acid:

To *N*-Boc-4-Fluoro-D-Phe (2.37g, 8.366 mmol), in MeOH, 3 mL of concentrated sulfuric acid was added. The reaction mixture was heated to reflux overnight then concentrated to dryness to afford the title compound. EIS-MS 198 [M+1].

10

B. Ethoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid:

To a 0°C mixture of material from part A (1.65 g, 8.37 mmol) and pyridine (1.35 mL, 17.4 mmol), in DCM, was slowly added ethyl chloroformate (0.85 mL, 8.87 mmol).

15 After 30 minutes the mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (2X). The combined organic extracts were dried (MgSO₄) and concentrated to dryness to afford 2.17g (96%) of the title compound. EIS-MS 270 [M+1].

20 C. 7-Fluoro-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-ethyl ester:

A mixture of material from part B (2.17g, 8.06 mmol), paraformaldehyde (0.254g, 8.46 mmol), and 10 mL of 3:1 glacial acetic acid/concentrated sulfuric acid was stirred at room temperature for 48 h. The mixture was then partitioned between water and EtOAc.

25 The organic portion was separated and the aqueous layer extracted with EtOAc(3X). The combined EtOAc extracts were dried(MgSO₄), and concentrated to dryness. Flash chromatography of the resulting residue (SiO₂, eluting with 25% EtOAc/Hexane); affording 1.31g (58%) of the title compound. EIS-MS 282 [M+1].

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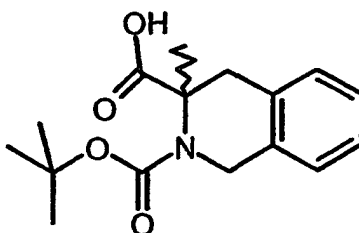
D. 7-Fluoro-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid:

The product from Part C (1.31g, 4.656 mmol), in 20 mL of 5N HCl, was heated at reflux for 24 h. The solution was then concentrated to dryness. The resulting white solid
5 was washed with Et₂O to afford 0.87g (81%) of the title compound. EIS-MS 196 [M+1].

E. To the product from part D (0.87g, 3.75 mmol), in 20 ml of 1:1 dioxane/water, was added Di-*t*-butyl-dicarbonate (0.90g, 4.13 mmol) and TEA (2.36 mL, 16.90 mmol). The mixture was stirred at room temperature for 16 h and then diluted with EtOAc. The
10 organic portion was separated and the aqueous layer extracted with EtOAc (3X). The combined organic portions were dried (MgSO₄) and concentrated to dryness to give 0.64g (58%) of the title compound. EIS-MS 294 [M+1].

Preparation C10

15 3-Methyl-3,4-dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester

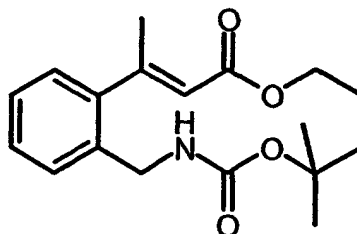


The compound of Preparation C10 was prepared from -methyl-D,L-Phe by following the substantially similar procedure described in Preparation C9; yielding 1.7 g,
20 of the title compound. EIS-MS 292 [M+1].

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Preparation C11

3-[2-(tert-Butoxycarbonylamino-methyl)-phenyl]-but-2-enoic acid ethyl ester

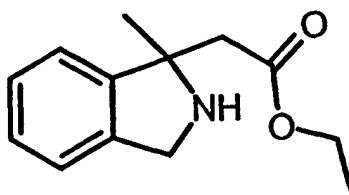


- 5 *N*-Boc-2-bromobenzylamine (7.15 g, 25 mmol) was dissolved into tributylamine (12 mL) and degassed under vacuum. Palladium acetate (224 mg, 1 mmol) and tri-*o*-tolylphosphine (608 mg, 2 mmol) was then added and the mixture degassed under vacuum. Trans-ethylcrotonate (6.25 mL, 50 mmol) was then added and the mixture was degassed with nitrogen. The tube was sealed and the mixture was heated to 110°C for 48
- 10 h. The solution was cooled to room temperature, diluted with diethyl ether (200 mL) and filtered through celite. The solution was washed with 1*N* HCl (2 x 50 mL) and brine (50 mL) dried over magnesium sulfate and concentrated to dryness. Flash chromatography (9:1 hexanes/ ethyl acetate) gave the title compound as a yellow oil (1.6 g, 20%). ¹H
- 15 NMR 7.22-7.37 (m, 3H), 7.08 (dd, *J* = 7.4, 1.6 Hz, 1H), 5.75 (d, *J* = 1.3 Hz, 1H), 4.29-4.31 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.45 (d, *J* = 1.3 Hz, 3H), 1.44 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H).

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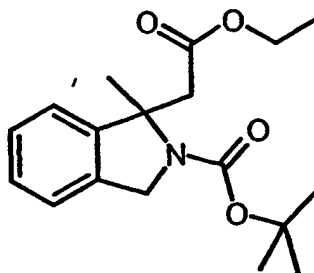
Preparation C12

(1-Methyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid ethyl ester



5 To Preparation C11 (1.6 g, 5 mmol), in CH_2Cl_2 was added TFA (10 mL). The mixture was stirred for 1 h at room temperature and concentrated to a yellow oil. TEA (5 mL) was added and the solution was stirred for 15 minutes and concentrated to dryness. Purification by flash chromatography (SiO_2 , eluting with 5% 2N NH_3 in MeOH/EtOAc) gave the title compound as a clear oil (1.0 g, 92%).

10

Preparation C131-Ethoxycarbonylmethyl-1-methyl-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester

15

(1-Methyl-2,3-dihydro-1H-isoindol-1-yl)-acetic acid ethyl ester (1.0 g, 4.6 mmol) and di-*tert*-butyl dicarbonate (1.1 g, 5.06 mmol) were dissolved into DCM (10 mL) under nitrogen atmosphere. The solution was cooled to 0 °C followed by dropwise addition of TEA (0.71 mL, 5.06 mmol). The solution was warmed to room temperature and stirred 72 h. DCM (50 mL) was added and the solution washed with saturated sodium bicarbonate (5 mL), H_2O (5 mL) and brine (5 mL). The organic phase was dried over magnesium sulfate and concentrated to a clear oil. Purification by flash chromatography (SiO_2) gave the title compound as a clear oil (1.18 g, 81%). ^1H NMR (CDCl_3) δ 7.10-

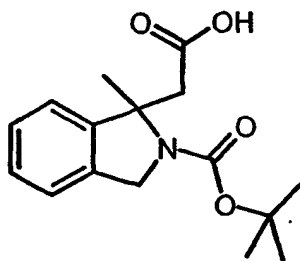
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7.30 (m, 4H), 4.65-4.70 (m, 2H), 3.84-3.92 (m, 2H), 3.42-3.48 (m, 0.5H), 2.65-2.80 (m, 1.5H), 1.75 (s, 1.6H), 1.68 (s, 1.4H), 1.55 (s, 5H), 1.48 (s, 4H).

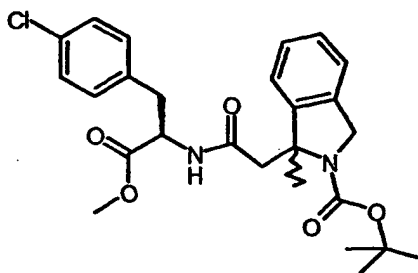
Preparation C14

5 1-Carboxymethyl-1-methyl-1,3-dihydro-isoindole-2-carboxylic acid *tert*-butyl ester



Compound of Preparation C13 (1.14 g, 3.56 mmol) was dissolved into ethanol (10 mL) and H₂O (2 mL) and cooled to 0°C. Lithium hydroxide (470 mg, 11.1 mmol) was added and the mixture was stirred at room temperature for 24 h. Lithium hydroxide (340 mg, 8 mmol) was added and the solution was stirred for about 24 h. A 1 N solution of NaOH (5 mL) was added and the solution was washed with hexanes (10 mL). The aqueous solution was acidified with 1N HCl to pH 1. The solution was extracted with EtOAc (3 x 20 mL), dried over magnesium sulfate and concentrated to a white solid. The residue was recrystallized from hexanes to give the title compound (850 mg, 82%). ¹H NMR (CDCl₃) δ 7.10-7.30 (m, 4H), 4.60 (s, 2H), 3.65-3.80 (m, 0.6H), 3.30-3.40 (m, 0.4H), 2.70-2.80 (m, 1H), 1.65-1.75 (m, 3H), 1.45-1.60 (m, 9H).

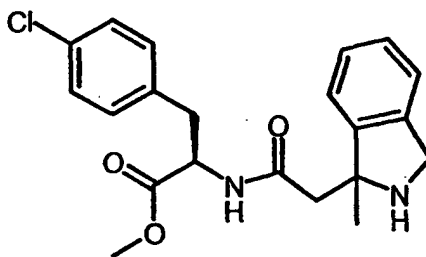
-117-

Preparation BC4

To 4-Chloro-D-Phenylalanine methyl ester hydrochloride (0.432 g, 1.73 mmol) was added Compound of preparation C13 (0.504 g, 1.73 mmol), EDC (0.330 g, 1.73 mmol) and HOBT (0.233 g, 1.73 mmol). This was followed by addition of dichloromethane (5 mL) and DIPEA (0.452 mL). The solution was stirred for 3 h then diluted with EtOAc (50 mL). The organics were washed with saturated NaHCO₃ (50 mL), water (50 mL), and concentrated to dryness. The crude product was purified by flash chromatography (SiO₂, eluting with Hexane/EtOAc, 80:20) yielding 0.724 g, 86% of the title compound as a white solid. EIS-MS 487.2 [M+1].

Preparation BC5

3-(4-Chloro-phenyl)-2-[2-(1-methyl-2,3-dihydro-1H-isoindol-1-yl)-acetylamino]-propionic acid methyl ester



15

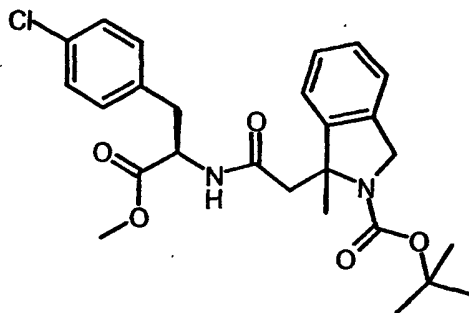
To compound of Preparation BC4 in DCM (3 mL), was added TFA (3 mL) and the mixture was allowed to stand for 2h. After concentrating to dryness, the diastereomers were separated by reverse phase HPLC [Waters Symmetry C18 column, eluting with H₂O(0.05%HCl)/CH₃CN, 90:10 to 60:40, following a straight line gradient]. The first eluting isomer was labeled isomer 1 and the second isomer 2. EIS-MS 387.1 [M+1] for both isomers.

20

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Preparation BC6

1-{{2-(4-Chloro-phenyl)-1-methoxycarbonyl-ethylcarbamoyl]-methyl}-1-methyl-1,3-dihydro-isindole-2-carboxylic acid tert-butyl ester, isomer 1



5

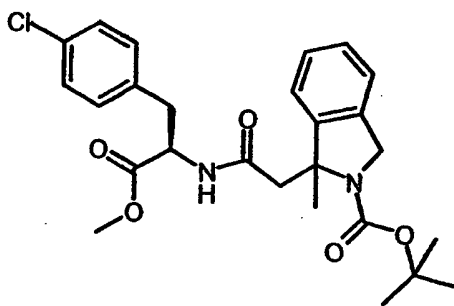
To the compound of Preparation BC5 (isomer 1, 0.321 g, 0.831 mmol), in THF/H₂O 1:1, 4 mL) was added K₂CO₃ (0.253 g, 1.83 mmol) and BOC₂O. The mixture stirred for 12 h and then the crude mixture was diluted with EtOAc (25 mL), the organics washed with H₂O and concentrated to dryness; yielding the title compound (0.33 g, 81%).

10 EIS-MS 487.1 [M+1].

Preparation BC7

1-{{2-(4-Chloro-phenyl)-1-methoxycarbonyl-ethylcarbamoyl]-methyl}-1-methyl-1,3-dihydro-isindole-2-carboxylic acid tert-butyl ester, isomer 2

15



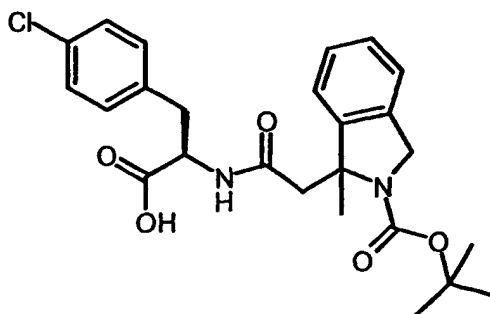
The compound of Preparation BC7 was prepared from the compound of Preparation BC5 (isomer 2) by following the substantially similar procedure described in Preparation BC6.

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Preparation BC8

1-[[1-Carboxy-2-(4-chloro-phenyl)-ethylcarbamoyl]-methyl}-1-methyl-1,3-dihydro-
isoindole-2-carboxylic acid tert-butyl ester, isomer 1

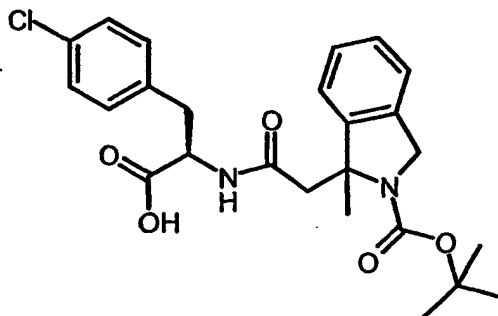


5 To the product from Preparation BC6 (isomer 1, 0.330 g, 0.679 mmol) in
H₂O/THF 1:1 (10 mL) was added LiOH (0.050 g, 2.01 mmol). The mixture was stirred
for 5 h, then diluted with H₂O (50 mL) and acidified to pH 4 with 25% KHSO₄. The
aqueous mixture was extracted with EtOAc (100 mL) and concentrated to dryness;
yielding the title compound (0.335 g). EIS-MS 473.2 [M+1].

10

Preparation BC9

1-[[1-Carboxy-2-(4-chloro-phenyl)-ethylcarbamoyl]-methyl}-1-methyl-1,3-dihydro-
isoindole-2-carboxylic acid tert-butyl ester, isomer 2



15

Preparation BC9 was prepared from the compound of Preparation BC7 (isomer 2)
by following the substantially similar procedure described in Preparation BC8; yielding
0.26 g, 95% of the title compound.

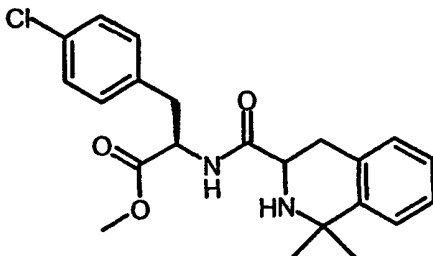
EIS-MS 473.3 [M+1].

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Preparation BC10

3-(4-Chloro-phenyl)-2-[(1,1-dimethyl-1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)-amino]-propionic acid methyl ester



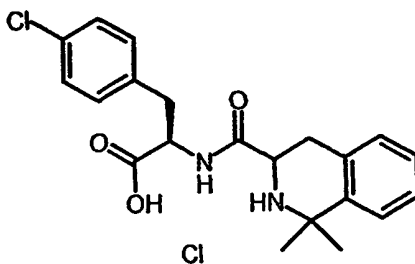
5

To a solution of 1,1-dimethyl TIC (240 mg, 1.17 mmol), 4-Cl-D-Phe methyl ester (322 mg, 1.28 mmol), HOBT (197 mg, 1.46 mmol), and DIPEA (0.81 mL, 44.68 mmol, 4.0 eq) in CH₂Cl₂/DMF (1:1) was added EDC (280 mg, 1.46 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc (100 mL), washed with saturated aqueous NaHCO₃, brine, dried (Na₂SO₄) and concentrated to dryness. Purification and separation of diastereomers by flash chromatography (35 g SiO₂, linear gradient, 40 mL/min 10-50% EtOAc/hexane for 25 minutes and 50% EtOAc/hexane for 7 minutes) afforded title compound.

15

Preparation BC11

3-(4-Chloro-phenyl)-2-[(1,1-dimethyl-1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)-amino]-propionic acid



20

To Preparation BC10 (5.95 g, 14.88 mmol), in a 1:1 mixture of THF/H₂O (50 mL), was added lithium hydroxide hydrate (0.75 g, 17.87 mmol). The reaction was stirred at room temperature for 18 h. The mixture was then concentrated to dryness. The

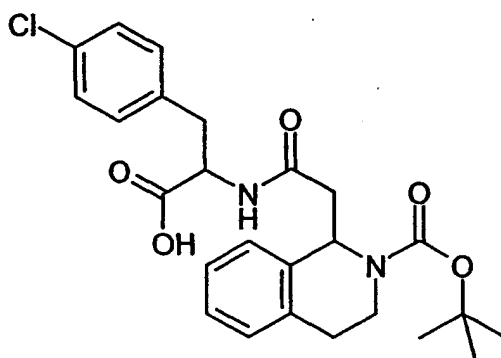
-121-

resulting residue was dissolved in water (50 mL), made acidic with 1N HCl (25 mL) and washed with Et₂O (100 mL). The aqueous layer was evaporated to dryness, yielding 6.18 g (98%) of the title compound. EIS-MS 387 [M+1].

5

Preparation BC12

1-{[1-Carboxy-2-(4-chloro-phenyl)-ethylcarbamoyl]-methyl}-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, isomer 1



10

A. To a solution of D-4-chlorophenylalanine methyl ester hydrochloride (883 mg, 3.53 mmol), Preparation C3 (isomer 1) (1.0 g, 3.36 mmol), HOBT (568 mg, 4.2 mmol), and DIPEA (2.92 mL, 16.8 mmol) in CH₂Cl₂ (35 mL) was added EDC (805 mg, 4.2 mmol). The resulting mixture was stirred at room temperature for 48h. The reaction mixture was poured into a mixture CH₂Cl₂-water (1:1) and the organic phase washed with

15 water (2x), dried (Na₂SO₄), filtered, and concentrated to dryness. Final purification by flash chromatography EtOAc-hexane (3:7) afforded 1.38 g of desired compound as a white solid. MS m/z 485.2 (M⁺-1)

20

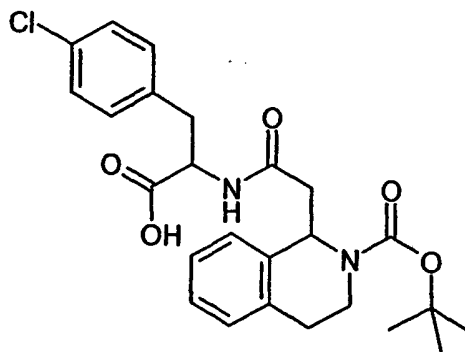
B. To a solution of the above-formed ester (1.38 g, 2.83 mmol) in THF (15 mL), a 1M aqueous solution of LiOH·H₂O (14.15 mL, 14.15 mmol) was added and mixture stirred at room temperature for 1h. Reaction was cooled to 0°C and pH was adjusted to ≈1 upon addition of 1M HCl. Aqueous layer was extracted with EtOAc, dried (Na₂SO₄), and evaporated to afford 1.32 g of the title compound as a white solid. MS m/z 471.2 (M⁺-1)

25

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Preparation BC13

1-[[1-Carboxy-2-(4-chloro-phenyl)-ethylcarbamoyl]-methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, isomer 2



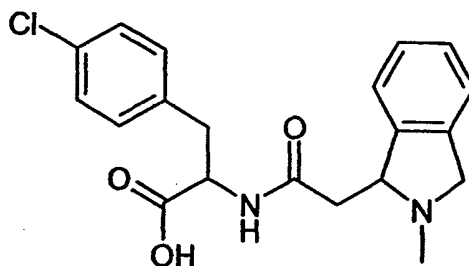
5

The compound of Preparation BC13 was prepared from Preparation C3 (isomer 2) by following a procedure substantially similar to that described in Preparation BC12. MS m/z 471.2 (M^+-1)

10

Preparation BC14

3-(4-Chloro-phenyl)-2-[2-(2-methyl-2,3-dihydro-1H-isoindol-1-yl)-acetylamino]-propionic acid



15

A. To a solution of D-4-chlorophenylalanine methyl ester hydrochloride (1.37 g, 5.49 mmol), Preparation C6 (1.2 g, 5.23 mmol), HOBT (883 mg, 6.54 mmol), and DIPEA (4.55 mL, 26.2 mmol) in CH_2Cl_2 (35 mL) was added EDC (1.25 g, 6.54 mmol). The resulting mixture was stirred at room temperature for 48h. The reaction mixture was poured onto a mixture CH_2Cl_2 -water (1:1) and the organic phase washed with water (2x), dried (Na_2SO_4), filtered, and concentrated to dryness. Final purification by flash

20

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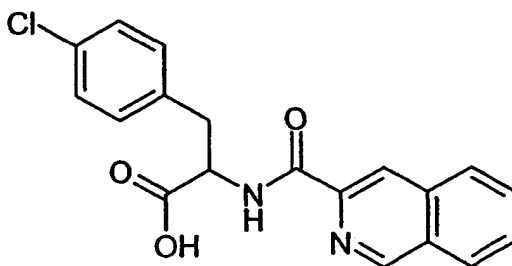
chromatography (EtOAc, then EtOAc/MeOH/AcOH 95:5:5) afforded 1.71 g of desired compound as a solid. MS m/z 387.1 ($M^+ + 1$)

5 B. To a solution of the above-formed ester (1.71 g, 4.4 mmol) in THF (40 mL), a 1M aqueous solution of LiOH·H₂O (22.1 mL, 22.1 mmol) was added and mixture stirred at room temperature for 1h. Reaction was cooled to 0°C and pH was adjusted to ≈1 upon addition of 1M HCl. Aqueous layer was extracted with EtOAc, dried (Na₂SO₄), and evaporated to afford 1.6 g of the title compound as a solid. MS m/z 373.2 ($M^+ + 1$)

10

Preparation BC15

3-(4-Chloro-phenyl)-2-[(isoquinoline-3-carbonyl)-amino]-propionic acid



15 A. To a solution of D-4-chlorophenylalanine methyl ester hydrochloride (758 Mg, 3.03 mmol), 3-isoquinolinecarboxylic acid hydrate (500 mg, 2.89 mmol), HOBT (488 mg, 3.61 mmol), and DIPEA (2.51 mL, 14.45 mmol) in CH₂Cl₂ (30 mL) was added EDC (692 g, 3.61 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured onto a mixture EtOAc (150 mL) and water (20 mL) and the organic phase washed with water (3x), dried (Na₂SO₄), filtered, and
20 concentrated to dryness. Final purification by flash chromatography (EtOAc/hexane 1:2) afforded 820 mg of desired compound as a solid. MS m/z 369.1 ($M^+ + 1$).

25 B. To a solution of the above-formed ester (820 mg, 2.26 mmol) in THF (10 mL), a 1M aqueous solution of LiOH·H₂O (11.3 mL, 11.3 mmol) was added and mixture stirred at room temperature for 1h. Reaction was cooled to 0°C and pH was adjusted to ≈1 upon addition of 1M HCl. Aqueous layer was extracted with EtOAc, dried (Na₂SO₄), and evaporated to afford 790 mg of the title compound as a solid. MS m/z 353.0 ($M^+ - 1$)

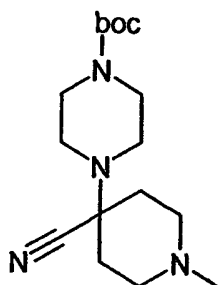
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Procedures for preparing A-domain pieces

Procedure I

Preparation 1A

5



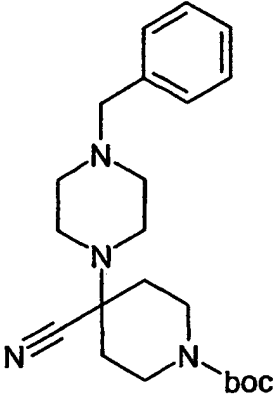
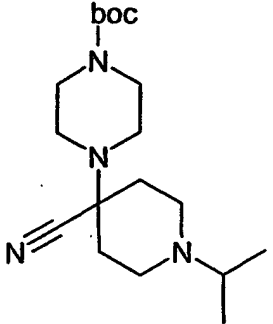
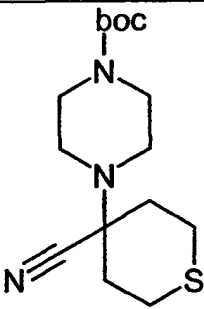
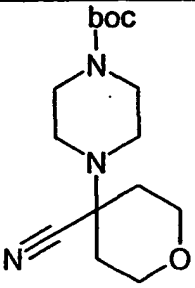
To a flask was added 1-Methyl-piperidin-4-one (5.00 g, 44.25 mmol), Trimethylsilyl cyanide (TMSCN) (4.38 g, 44.23 mmol) and Diethyl ether (5 mL) followed by addition of Zinc iodide (0.010 g, cat.) the subsequent exothermic reaction was controlled with an ice bath. The mixture was stirred at rt. for 15 minutes. To the solution was added a solution of Boc-piperazine (8.23 g, 44.23 mmol) in Methanol (60 mL). The solution was then refluxed for 3 h and stirred at room temperature for 12h. the solution was then concentrated to dryness and crystallized from EtOAc/Hexane. Yielding compound 1A (9.08 g, 67%). ES MS 309.3

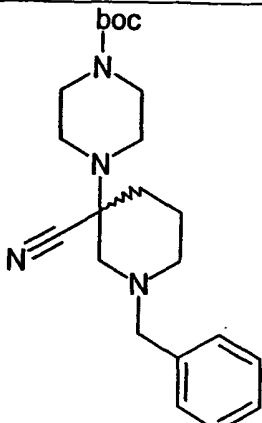
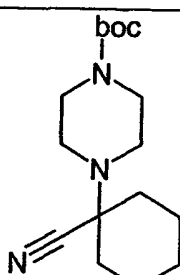
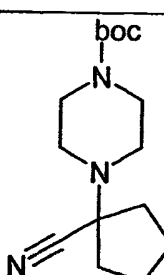
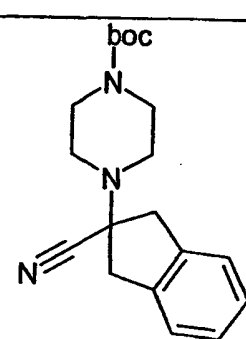
15 Compounds 2A-10A were prepared from a mono-protected piperazine and the appropriate ketone by procedures substantial similar to that of procedure I.

Table A

Preparation	Structure	ES MS (M + 1)
	<chem>CN1CC[C@]2(C#N)CCN(C2)N3CCN(C3)C(=O)OCC4=CC=CC=C4</chem>	

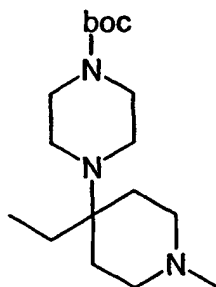
-125-

Preparation	Structure	ES MS (M + 1)
2A		428.2
3A		385.3
4A		337.3
5A		312.2
6A		296.2

Preparation	Structure	ES MS (M + 1)
7A		385.2
8A		394.2
9A		253.2
10A		

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Procedure II
Preparation 1B



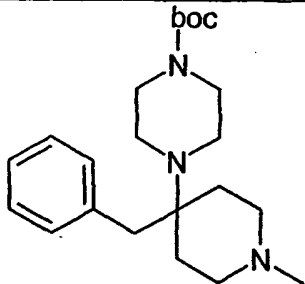
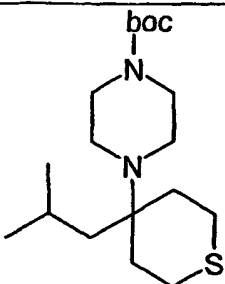
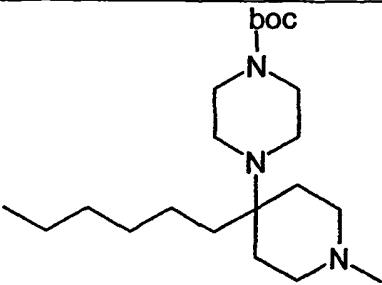
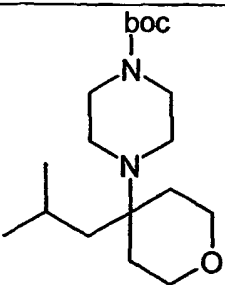
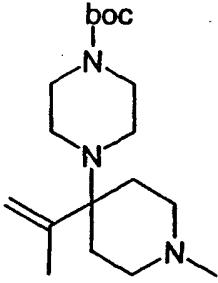
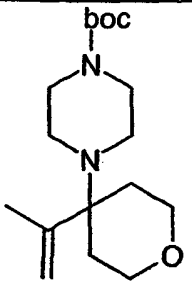
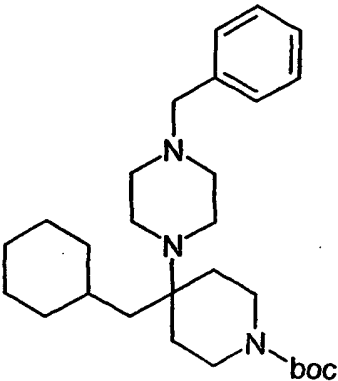
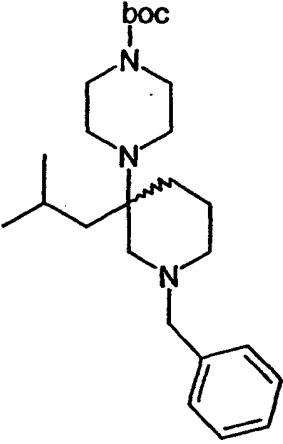
- 5 To a solution of Preparation 1A (0.500 g, 1.62 mmol) in THF (4.0 mL) was added ethyl magnesium bromide 3 molar in Et₂O (1.62 mL, 4.87 mmol). After stirring for 18 h the mixture was quenched by being poured into water (50 mL). The mixture was extracted with EtOAc (100 mL) and washed once with brine. Then concentrated to dryness yielding a yellow oil. Purification using Silica gel (60 mesh) eluting with
- 10 CHCl₃:MeOH (9:1) yielded compound 1B as a clear oil (0.119 g, 24%) ES MS (M+1) = 312.3

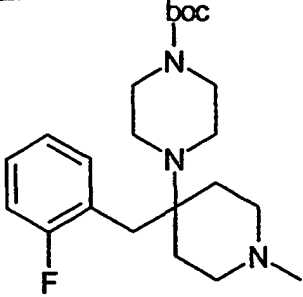
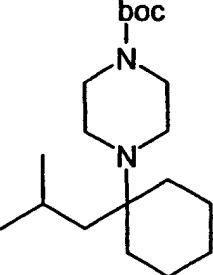
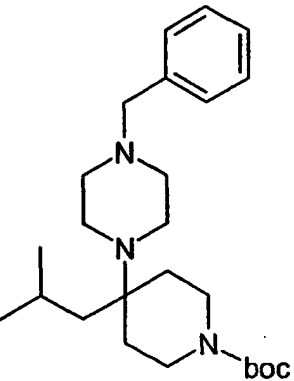
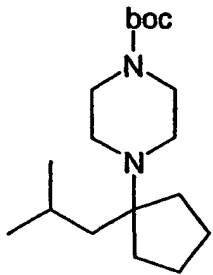
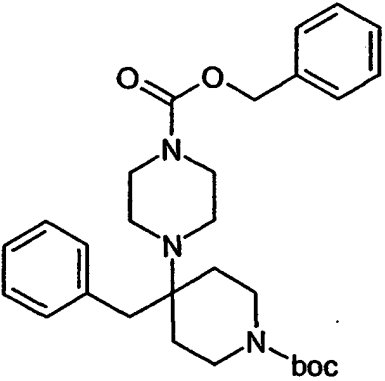
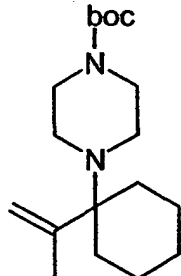
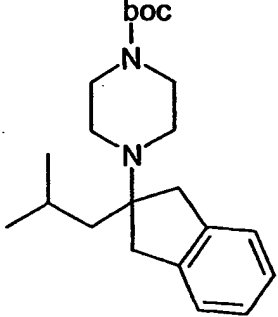
- The compounds of examples 2B-18B shown in table B below, were prepared from the appropriate amino nitrile (1A-10A) by procedures substantially similar to the preparation of 1B. Where the grignard was not commercial, it was synthesized from the
- 15 appropriate alkyl halide and magnesium turnings in either THF or Et₂O by common literature procedures.

Table B

Prep.	Compound	ES MS (M+1)	Prep.	Compound	ES MS (M+1)
2B		360.4	10B		368.4

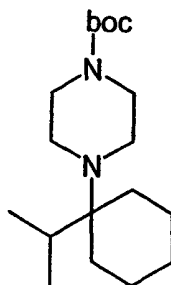
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Prep.	Compound	ES MS (M+1)	Prep.	Compound	ES MS (M+1)
3B		374.4	11B		343.3
4B		368.4	12B		327.3
5B		324.3	13B		311.3
6B		456.4	14B		416.3

Prep.	Compound	ES MS (M+1)	Prep.	Compound	ES MS (M+1)
7B		392.3	15B		325.3
8B		416.4	16B		311.3
9B		494.4	17B		309.3
			18B		359

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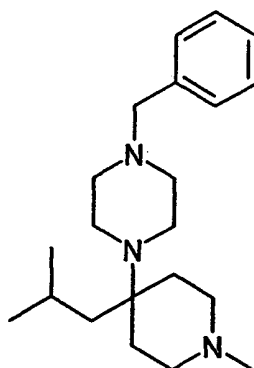
Procedure III

Preparation 11C

To a solution of compound 16B (0.164 g, 0.532 mmol) in EtOH (10 mL) was
5 added a slurry of 20% Pt on carbon (0.164 g) in EtOH (10 mL). The mixture was then
charged with H₂ gas via balloon. After vigorous stirring for 4 h the reaction atmosphere
was exchanged for N₂ gas. The mixture was filtered through a pad of Celite (~5 g) and
solvent was removed in vacuo yielding compound 11C (0.133 g, 81%) as pure product.

10

Procedure IV

Preparation 3C

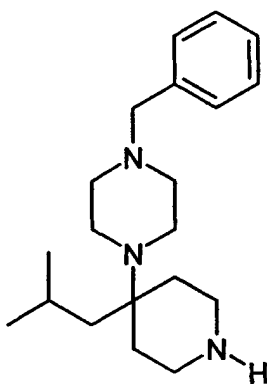
To a slurry of LAH (2.148g, 56.59 mmol) in THF (100 mL) at room temperature
15 was added compound 8B (11.76g, 28.30 mmol) in THF (100 mL) dropwise. The reaction
was allowed to stir at room temperature for 18 h then heated to reflux for 5 h. The
reaction mixture was cooled to 0°C and quenched carefully with water (8 mL), 15%
NaOH (8 mL) and water (26 mL). The mixture was stirred at room temperature for 1 hr,
then filtered. The filtrate was then concentrated *in vacuo*. The residue was partitioned
20 between water and ethyl acetate. The ethyl acetate layer was separated and dried over

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anhydrous sodium sulfate. Then filtered and concentrated *in vacuo*. The crude product was purified by chromatography using 5% 2M NH₃ in MeOH / 95% EtOAc as mobile phase to afford 3.24 g (38%) of pure compound.

5

Procedure V

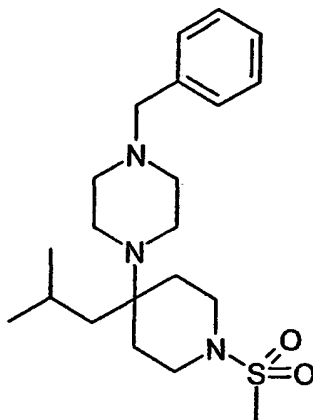
Preparation 4C

To a solution of compound 8B (2.330 g, 5.614 mmol) in CH₂Cl₂ (10 mL) was
10 added TFA (10 mL). The solution sat for 2 h followed by concentration in vacuo. The resulting residue was diluted with water (100 mL) and made alkaline with 1M NaOH (100 mL). The aqueous phase was extracted with EtOAc (100 mL), separated and concentrated in vacuo. Compound 4C was obtained cleanly as an oil (1.72 g, 97%).

15

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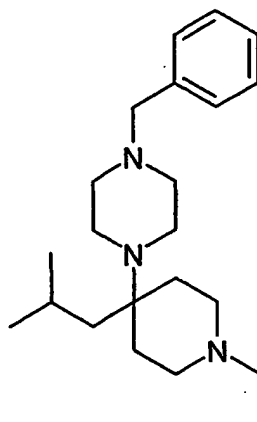
Procedure VI

Preparation 5C

- 5 To a solution of compound 4C (0.108 g, 0.347 mmol) in THF at 0°C was added DIPEA (0.066 mL, 0.377 mmol) followed by Methanesulfonyl chloride (0.26 mL, 0.347 mmol). The solution was allowed to warm to room temperature and stir for 4 h. The solution was diluted with EtOAc (50 mL) and washed with water (100 mL). The EtOAc was separated and concentrated in vacuo. The resulting crude material was purified by
- 10 column chromatography using silica gel (60 mesh) eluting with CHCl₃/MeOH (95/5). Compound 5C was collected cleanly (0.130 g, 88%)

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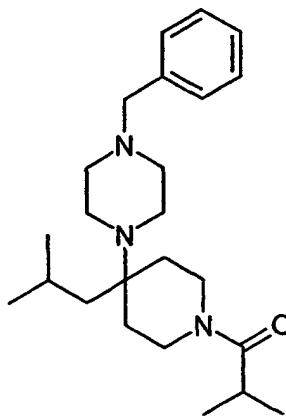
Procedure VII

Preparation 6C

5 To a solution of compound 4C (0.242 g, 0.768 mmol) in DMF (2.0 mL) was added K_2CO_3 (0.424 g, 3.073 mmol) and Bromoethane (0.115 mL, 1.537 mmol). The mixture was stirred overnight, diluted with EtOAc (40 mL) and washed with water 3X (20 mL). The EtOAc was separated then concentrated in vacuo. Compound 6C was collected cleanly without further purification (0.218 g, 75%)

10

Procedure VIII

Preparation 7C

15 To a solution of compound 4C (0.700 g, 2.22 mmol) in CH_2Cl_2 was added isobutyric acid (0.21 mL, 2.22 mmol), EDCI (0.426 g, 2.22 mmol) and DMAP (0.005 g, cat.). The solution was stirred for 1 h followed by dilution with EtOAc (100 mL) and

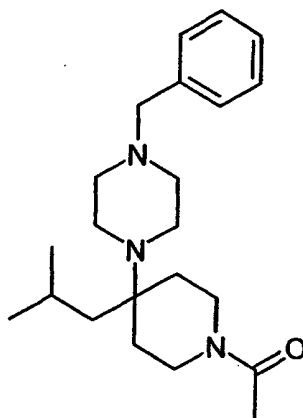
-134-

washed with water (100 mL). Compound 7C was collected cleanly and used with out further purification (0.83 g, 97%).

Procedure IX

Preparation 8C

5

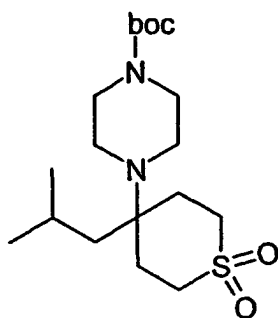


To compound 4C (0.387g, 1.23 mmol) was added Ac₂O (5 mL) and pyridine (5 mL). The mixture was heated at 65°C for 1h and then allowed to cool to room temperature. After diluting with EtOAc (100 mL) the organics were washed with saturated NaHCO₃, H₂O, brine and then concentrated to dryness to afford 305mg, 70% of compound 8C.

10

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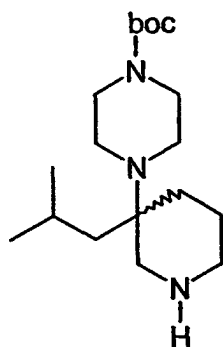
Procedure X

Preparation 9C

5 To compound 10B (5.00 g, 14.62 mmol) in CH_2Cl_2 (200 mL) was added methane sulfonic acid and let stir for 5 min. 3-chloroperoxybenzoic acid (70% pure) (7.18 g, 29.23 mmol) was then added portion wise. The mixture stirred for 2 h then poured into $\text{NaHCO}_3(\text{aq})$ (200 mL). The organics were separated, dried over K_2CO_3 and concentrated to dryness in vacuo to afford 4.59 g, 84% of high purity compound 9C.

10

Procedure XI

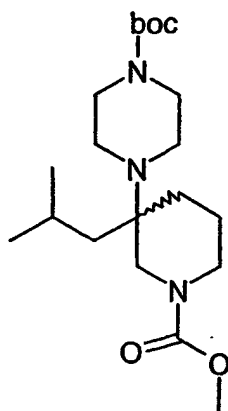
Preparation 12C

15 To compound 14B (3.06 g, 7.37 mmol) in EtOH (50 mL) was added a slurry of 10% Pd/C (3.06 g, 1 wt. Eq.) in EtOH (20 mL). The reaction atmosphere was exchanged via vacuum an H_2 balloon leaving the mixture under H_2 gas with vigorous stirring. After 5 h the H_2 gas was exchanged with N_2 gas. The mixture was filtered through celite and concentrated to dryness. Yield of Compound 12C was 2.07 g, or 86% of theory.

20

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Procedure XII

Preparation 13C

5 To compound 12C (1.00 g, 3.08 mmol) in THF/H₂O (8 mL/8 mL) was added NaOH (0.246 g, 6.16 mmol). To the mixture was added methyl chloroformate (0.26 mL, 3.38 mmol) dropwise. After vigorous stirring for 5 h the mixture was diluted with EtOAc (100 mL) and washed with water. The organics were separated and dried in vacuo. Compound 13C was collected and used without further purification. Yield: 1.17, 99% of
 10 theory.

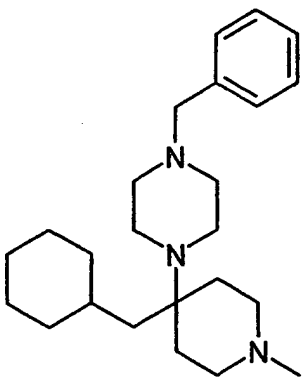
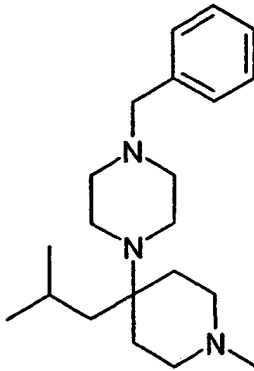
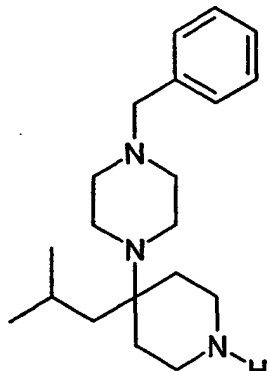
Compounds 1C-14C were prepared from the appropriate starting material and by following the procedures substantially similar to Procedures III through VIII.

Table C

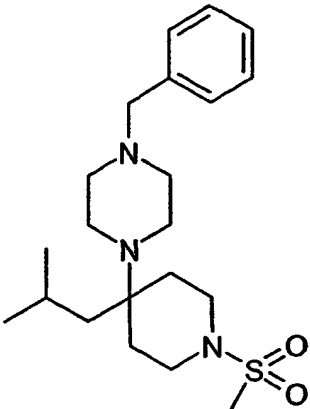
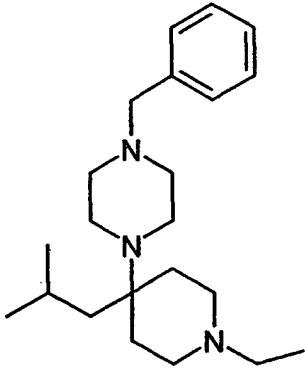
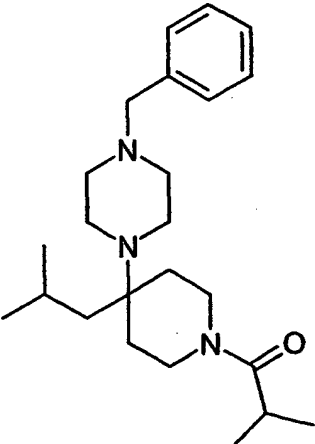
15

Example	Compound	ES MS (M + 1)	Starting From	Procedure
1C		326.3	5B	III

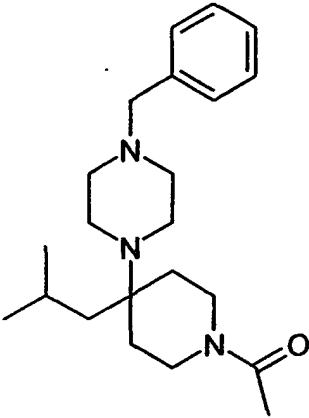
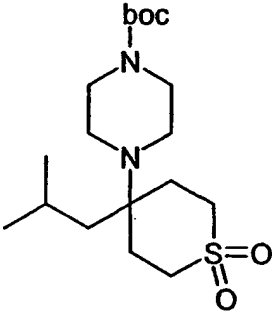
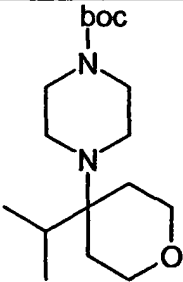
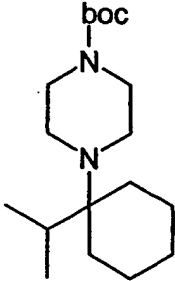
-137-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
2C		370.3	6B	IV
3C		330.3	8B	IV
4C		316.3	8B	V

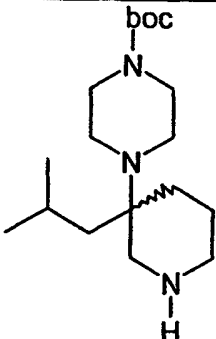
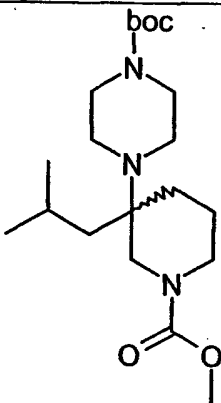
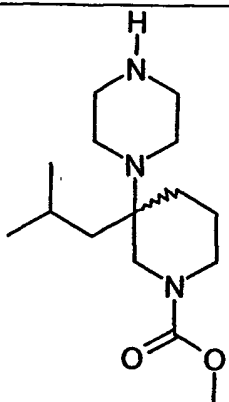
-138-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
5C		394.3	4C	VI
6C		344.4	4C	VII
7C		386.4	4C	VIII

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Example	Compound	ES MS (M + 1)	Starting From	Procedure
8C		358.3	4C	IX
9C		375.3	11B	X
10C		313.3	13B	III
11C		311.3	17B	III

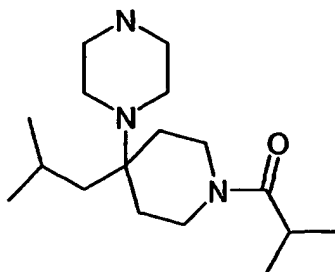
-140-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
12C		326.3	14B	XI
13C		384.3	12C	XII
14C		284.3	13C	V

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Procedure XIII

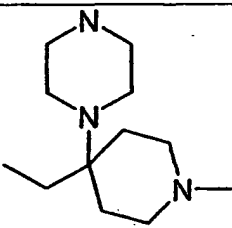
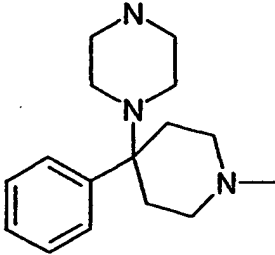
Preparation 19D



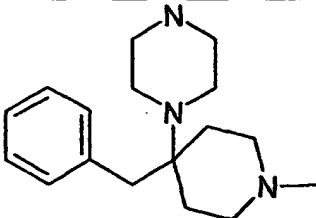
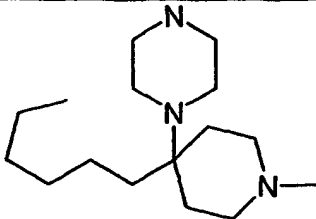
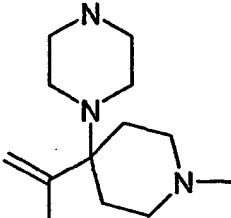
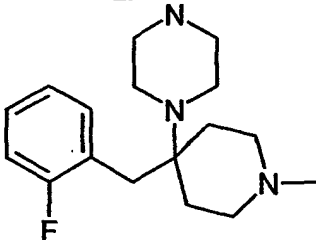
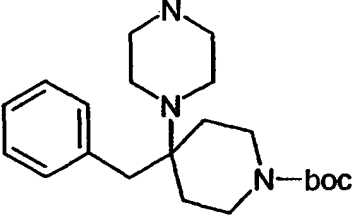
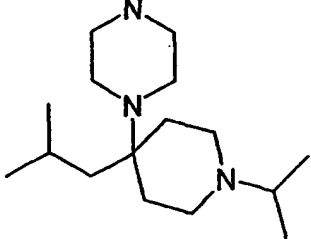
5 To Pd(OH)₂/C (20 wt.% on a dry basis, 300 mg) in EtOH (15 mL) was added compound 8C (0.304g, 0.85 mmol), in EtOH (10 mL). The mixture was stirred under H₂ (1 atm.) for 4h. The catalyst was removed by filtering over a pad of celite and the filtrate concentrated to dryness to afford 225mg, 99% of theory of compound 19D.

10 Compounds 1D-24D were prepared from the appropriate starting material and by following procedures substantially similar to the procedure indicated below.

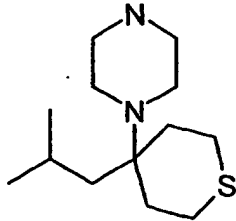
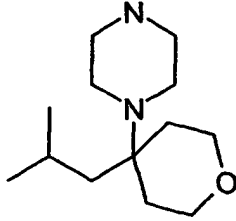
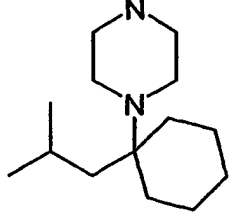
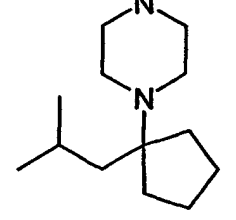
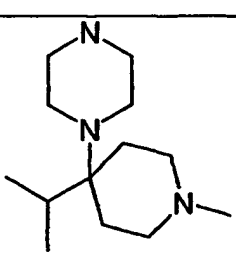
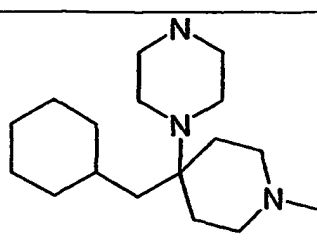
Table D

Example	Compound	ES MS (M+1)	Starting From	Procedure
1D		212.3	1B	V
2D		260.4	2B	V

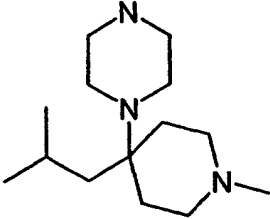
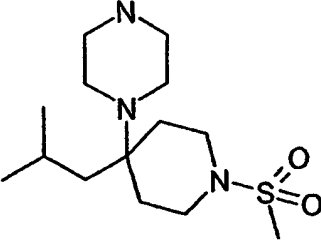
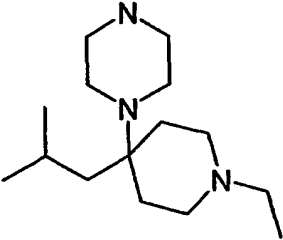
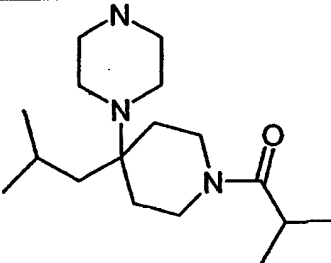
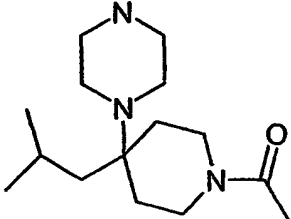
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Example	Compound	ES MS (M+1)	Starting From	Procedure
3D		274.4	3B	V
4D		268.4	4B	V
5D		224.3	5B	V
6D		292.3	7B	V
7D		360.2	9B	XIII
8D		268.4	10B	V

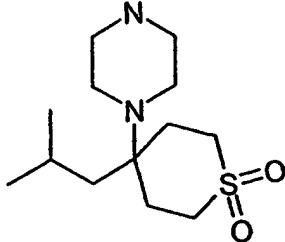
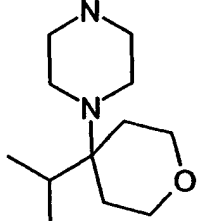
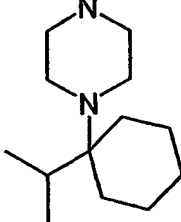
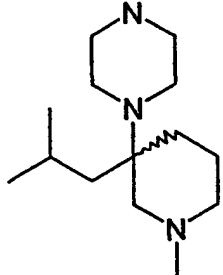
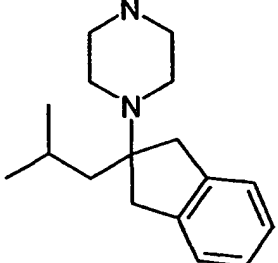
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Example	Compound	ES MS (M+1)	Starting From	Procedure
9D		243.3	11B	V
10D		227.3	12B	V
11D		225.3	15B	V
12D		211.3	16B	V
13D		226.3	1C	V
14D		280.3	2C	XI

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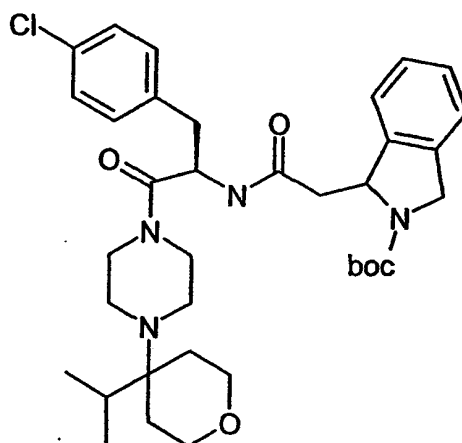
Example	Compound	ES MS (M+1)	Starting From	Procedure
15D		240.3	3C	XI
16D		304.2	5C	XIII
17D		254.3	6C	XIII
18D		295.3	7C	XIII
19D		268.2	8C	XIII

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Example	Compound	ES MS (M+1)	Starting From	Procedure
20D		275.3	9C	V
21D		213.3	10C	V
22D		211.3	11C	V
23D		240.2	14C	IV
24D		259	18B	V

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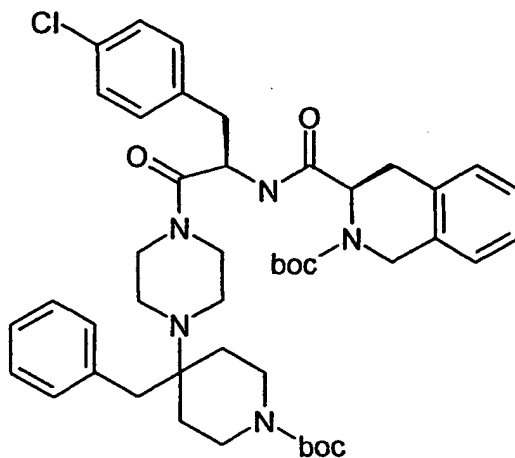
Procedure XIV

Example 18E

- 5 To Compound of preparation 21D (0.310g, 1.45 mmol) was added compound BC2 (0.669g, 1.45 mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.554g, 1.45 mmol), and CH₂Cl₂ (5mL). Diisopropylethylamine (1.27 mL, 7.29 mmol) was then added and the mixture stirred at room temperature for 3h.
- After diluting 10 fold with EtOAc the organics were washed with saturated
- 10 NaHCO₃, H₂O, brine, and concentrated to dryness. The desired product was purified by flash chromatography (SiO₂, eluting with 1:1 EtOAc/Hexanes to 100% EtOAc). Yield: 940mg, 99% of theory of compound of example 18E. Ion spray MS: 653.3 [M⁺].

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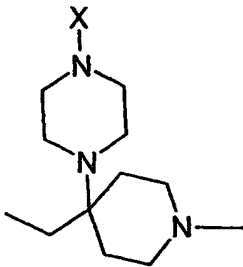
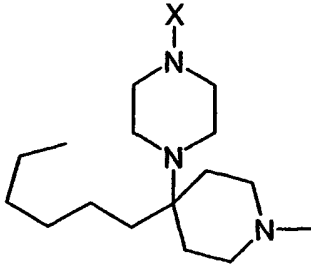
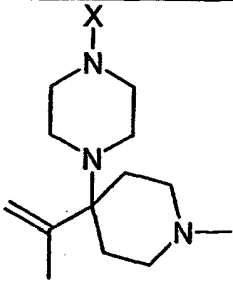
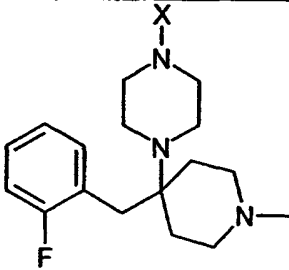
Procedure XV

Example 5E

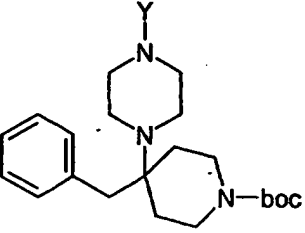
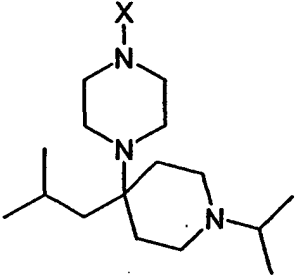
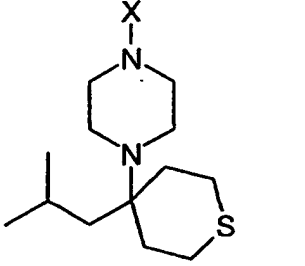
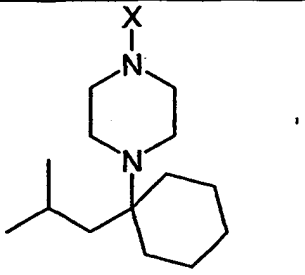
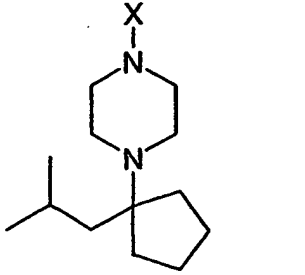
5 To Compound of Preparation 7D (0.274g, 0.763 mmol) was added compound of preparation BC1 (0.360g, 0.763 mmol), O-(7-Azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (0.290g, 0.763 mmol), and CH₂Cl₂ (4mL) and DMF (1 mL). Diisopropylethylamine (1.3 mL, 7.6 mmol) was then added and the mixture stirred at room temperature for 3h. After diluting 10 fold with EtOAc the
10 organics were washed with saturated NaHCO₃, H₂O, brine, and concentrated to dryness. The desired product was purified by flash chromatography (SiO₂, eluting with 7:3 Hexanes/EtOAc). The yield of compound of example 5E was 250 mg, or 41% of theory.

Compounds of examples 1E-20E were prepared from the appropriate N-substituted piperazines (1D-23D) and di-peptide acid (compound of preparation BC2 or
15 BC1) by following the procedures substantial similar to XIV and XV.

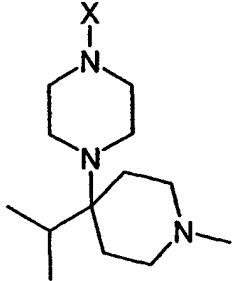
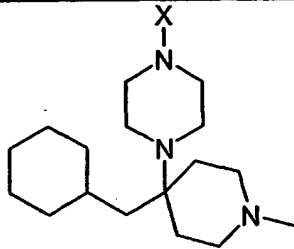
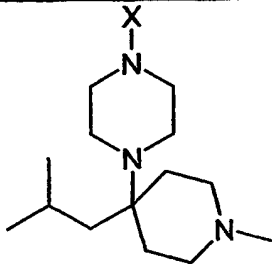
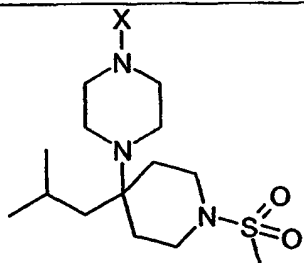
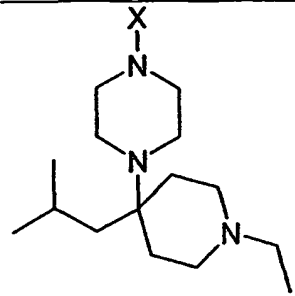
Table E

Example	Compound	ES MS (M + 1)	Starting From	Procedure
1E		652.4	1d	XIV, X = BC2 And Y = BCI
2E		708.4	4D	XIV
3E		664.4	5D	XIV
4E		732.4	6D	XIV

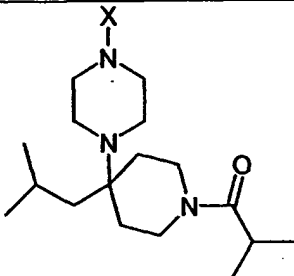
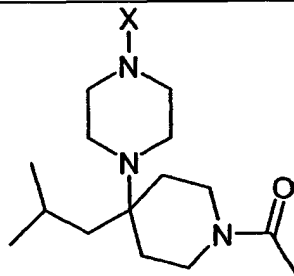
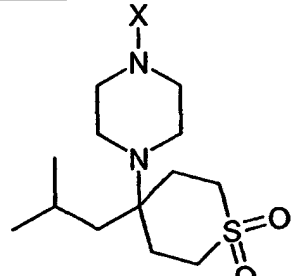
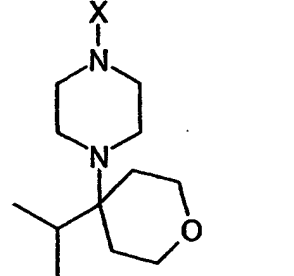
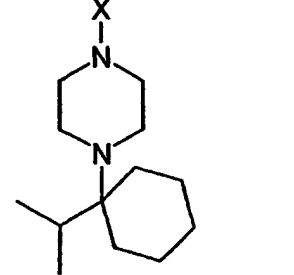
-149-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
5E		800.3	7D	XV
6E		708.4	8D	XIV
7E		683.3	9D	XIV
8E		665.3	11D	XIV
9E		651.3	12D	XIV

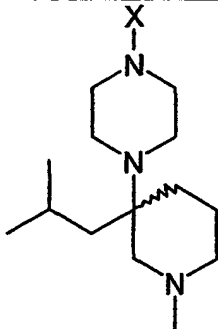
-150-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
10E		666.4	13D	XIV
11E		720.3	14D	XIV
12E		680.3	15D	XIV
13E		744.3	16D	XIV
14E		694.4	17D	XIV

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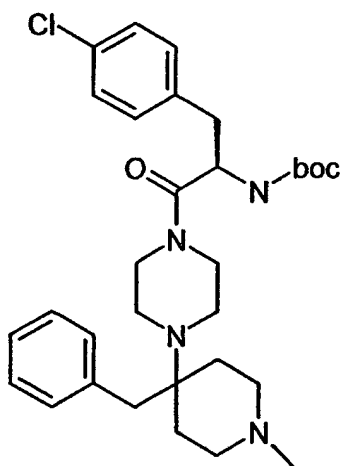
Example	Compound	ES MS (M + 1)	Starting From	Procedure
15E		736.2	18D	XIV
16E		708.3	19D	XIV
17E		715.3	20D	XIV
18E		653.3	21D	XIV
19E		651.3	22D	XIV

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Example	Compound	ES MS (M + 1)	Starting From	Procedure
20E		680.4	23D	XIV

Procedure XVI

Preparation 1F



5

To compound 3D (0.404 g, 1.48 mmol) in CH_2Cl_2 (2 mL) was added Boc-4-Chloro-D-Phe (0.440 g, 1.48 mmol), EDCI (0.284 g, 1.48 mmol) and HOBT (0.199 g, 1.48 mmol). The mixture was stirred for 1 h, then diluted with EtOAc (50 mL) and washed with water (50 mL). The organics were separated and concentrated to dryness in vacuo. The resulting oil was purified by column chromatography (silica gel 60) eluting with EtOAc 100% to 90:5:5 (EtOAc:MeOH:Et₃N). The yield of compound 1F was 0.775g, or 95% of theory.

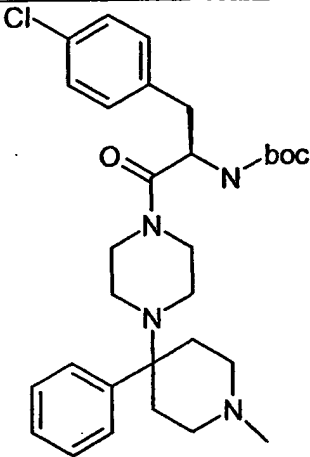
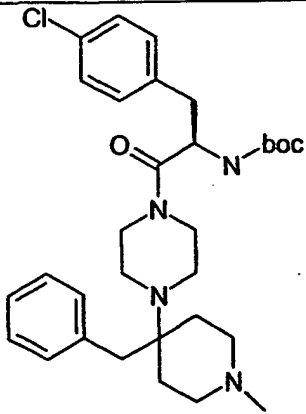
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-153-

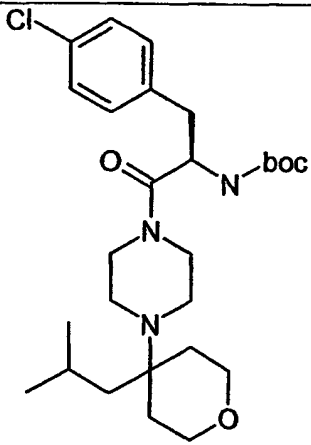
Compounds 1F-3F were prepared from the appropriate N-substituted piperazines (1D-23D) and (Boc-4-Chloro-D-Phe acid) by following the procedure substantially similar to the Procedure XVI.

5

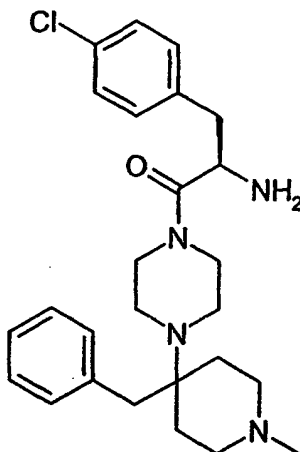
Table F

Example	Compound	ES MS (M + 1)	Starting From	Procedure
1F		541.4	2D	XVI
2F		555.3	3D	XVI

-154-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
3F		508.3	10D	XVI

Procedure XVII

Preparation 2G

5

To a solution of compound 2F (0.775 g, 1.40 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL). The solution sat for 2 h followed by concentration in vacuo. The resulting residue was diluted with water (20 mL) and made alkaline with 1M NaOH (20 mL). The aqueous phase was extracted with EtOAc (50 mL), separated and concentrated in vacuo.

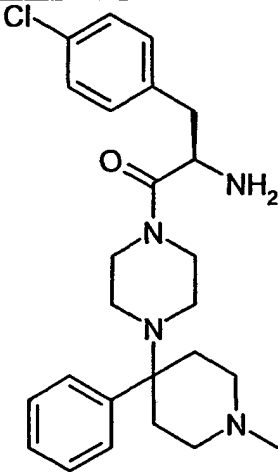
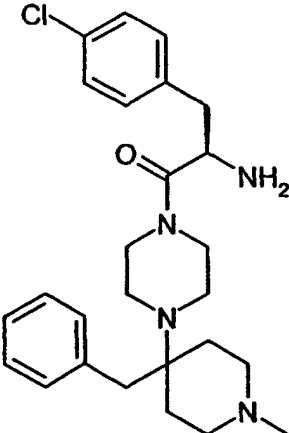
10 Compound 2G was collected cleanly as an oil (0.525 g, 83%).

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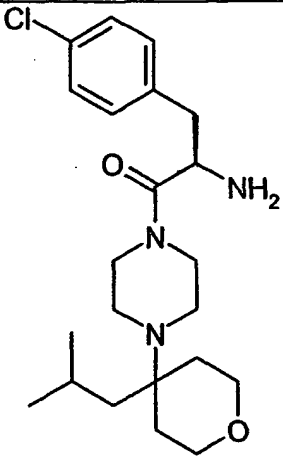
Compounds 1G-3G were prepared from 1F-3F by following the procedure substantially similar to Procedure XVII.

Table G

5

Example	Compound	ES MS (M + 1)	Starting From	Procedure
1G		441.4	1F	XVII
2G		455.3	2F	XVII

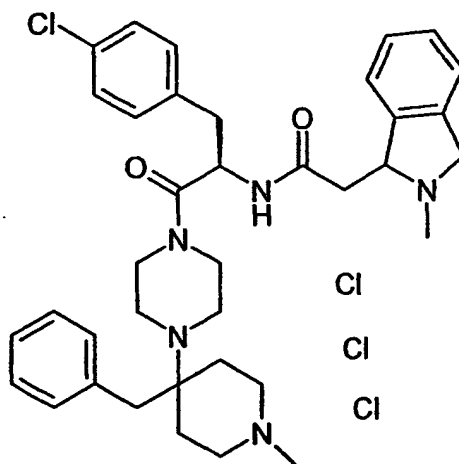
-156-

Example	Compound	ES MS (M + 1)	Starting From	Procedure
3G		408.3	3F	XVII

Procedure XVIII

Example 4H

- 5 N-[2-[4-(4-Benzyl-1-methyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-chloro-benzyl)-2-oxo-ethyl]-2-(2-methyl-2,3-dihydro-1H-isoxazol-1-yl)-acetamide (3HCl)



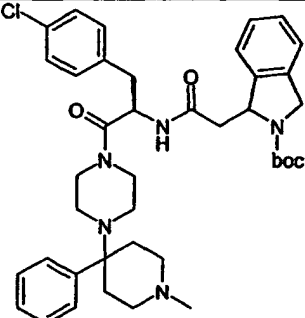
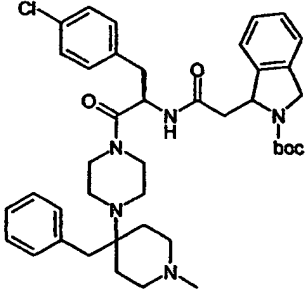
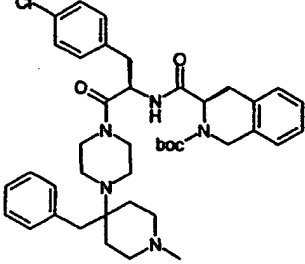
- To compound 2G (0.525 g, 1.15 mmol) in CH_2Cl_2 (5 mL) was added EDCI (0.242 g, 1.27 mmol), HOBT (0.171 g, 1.27 mmol) and C7 (0.291 g, 1.27 mmol). The solution was stirred for 4 h then diluted with EtOAc (50 mL). Washed sequentially with $\text{NaHCO}_3(\text{aq})$ (50 mL) and water (50 mL). The organics were separated and concentrated to dryness. The resulting oil was purified by reverse phase column chromatography using
- 10

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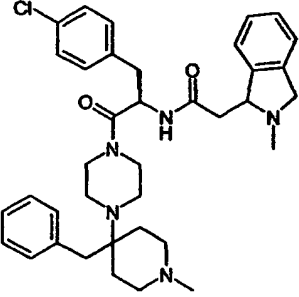
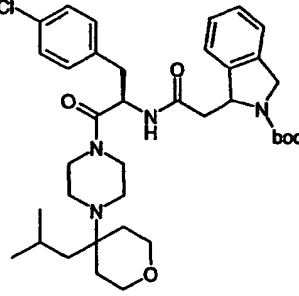
a symmetry C18 column eluting with water (HCl buffer .05% and CH₃CN) 90:10 to 70:30. Compound of example 4H was collected as the HCl salt (0.450 g, 60%)

Compounds of examples 1H-5H were prepared from the appropriate primary amine of 1G-3G and acids C7, C2 and Boc-D-Tic by using the procedures substantially similar to XVI and XVIII as noted in the following table.

Table H

Example	Compound	ES MS (M + 1)	Starting From	Procedure
1H		700.4	1G	XVI
2H		714.3	2G	XVI
3H		714.3	2G	XVI

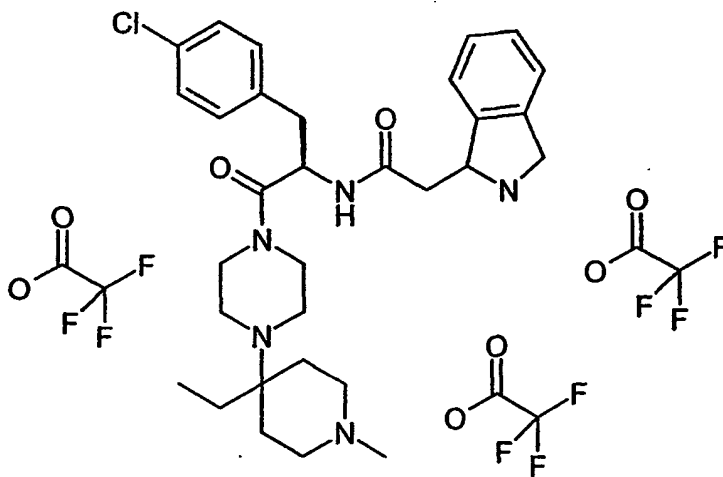
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Example	Compound	ES MS (M + 1)	Starting From	Procedure
4H		628.3	2G	XVIII
5H		667.3	3G	XVI

Procedure XIX

Example 11

- 5 N-{1-(4-Chloro-benzyl)-2-[4-(4-ethyl-1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxoethyl}-2-(2,3-dihydro-1H-indol-1-yl)-acetamide



To a solution of compound 1E (0.150 g, 0.230 mmol) in CH₂Cl₂ (1 mL) was
 10 added TFA (1 mL). The solution stirred for 1 hour. The solution was concentrated to

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dryness in vacuo. The resulting oil was then triturated with Et₂O. The Et₂O was decanted and the solid dried under vacuum. Compound 1I was collected as a white solid (0.127 g, 62% of theory)

ES MS (M+1) = 552.3

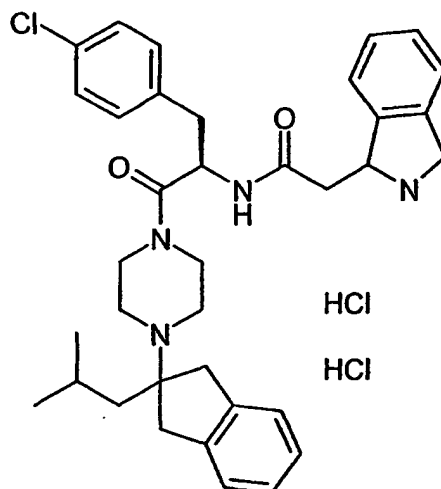
5

Procedure XX

Example 24I

N-{1-(4-Chloro-benzyl)-2-[4-(2-isobutyl-indan-2-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide dihydrochloride salt

10



A solution of compound 24D (360 mg, 1.09 mmol), N-Boc-isoindoline-4-Cl-D-Phe (537 mg, 1.25 mmol), 1-hydroxy-7-azabenzotriazole (185 mg, 1.36 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (516 mg, 1.36 mmol), and diisopropylethylamine (1.9 mL, 10.9 mmol) in CH₂Cl₂ (10 mL) and DMF (2.5 mL) was stirred at 23 °C for 16 h, diluted with CH₂Cl₂ and washed with brine, dried (Na₂SO₄), and evaporated. Purification by flash chromatography (hexane-EtOAc 4:1) gave rise to the coupled product. The Boc group was removed by stirring at room temperature in methylene chloride/TFA (1:1, 20 mL) for 2 hours. The solvent was evaporated and the residue purified by a SCX cartridge (MeOH→2M NH₃ in MeOH). The resulting oil was dissolved in 0.1 M HCl in EtOAc and stirred for 10 min. Final evaporation of the solvent afforded the desired product 2060431. MS m/z 599 (M⁺+1).

20

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Compounds of examples 2I-24I were prepared from the A-domain starting materials listed in table I below, using procedures substantially similar to Procedure XIX and XX. The hydrochloride salt can be prepared from the TFA salt by salt exchange in .5M HCl(aq) followed by lyophilization.

5

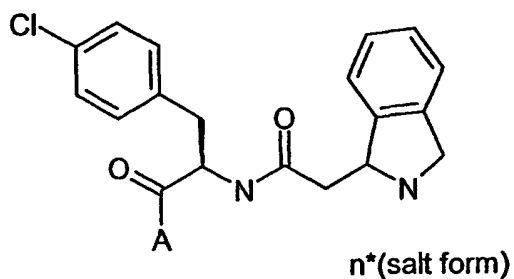
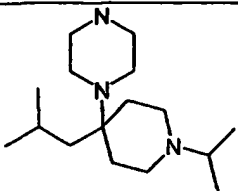
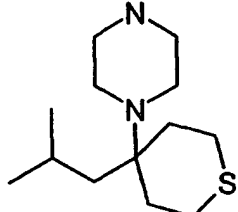
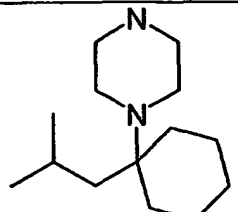
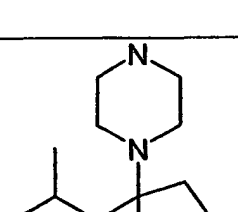
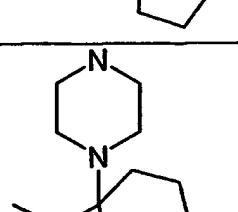
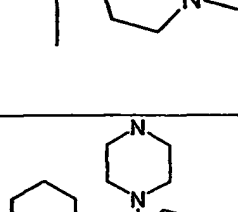


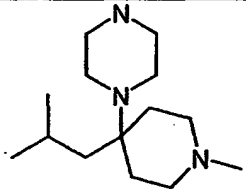
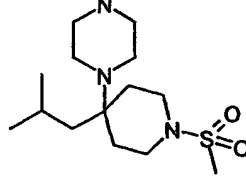
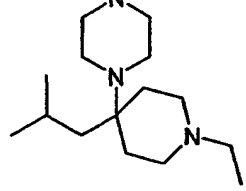
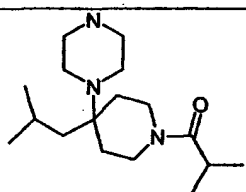
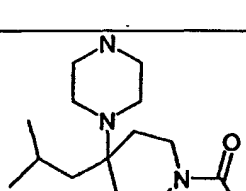
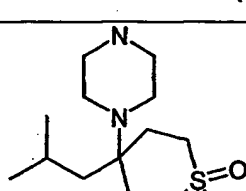
Table I

Example	A	ES MS (M + 1)	Starting From	Procedure	Salt Form
1I		552.3	1E	XIX	TFA
2I		608.3	2E	XIX	TFA
3I		564.3	3E	XIX	TFA
4I		632.3	4E	XIX	TFA

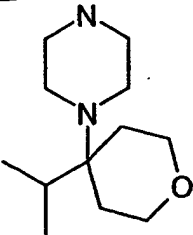
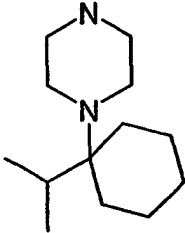
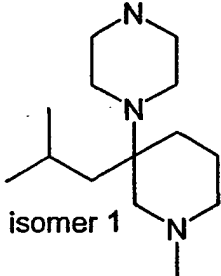
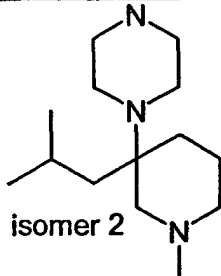
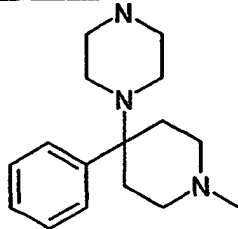
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Example	A	ES MS (M + 1)	Starting From	Procedure	Salt Form
5I		608.4	6E	XIX	TFA
6I		583.3	7E	XIX	TFA
7I		565.3	8E	XIX	TFA
8I		551.3	9E	XIX	TFA
9I		566.3	10E	XIX	TFA
10I		620.3	11E	XIX	HCl

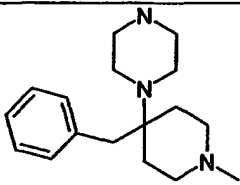
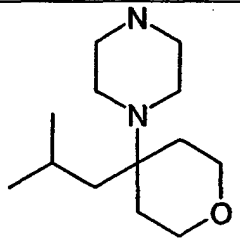
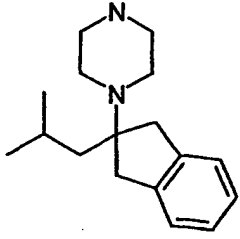
-162-

Example	A	ES MS (M + 1)	Starting From	Procedure	Salt Form
11I		580.3	12E	XIX	TFA
12I		644.3	13E	XIX	TFA
13I		594.4	14E	XIX	TFA
14I		636.3	15E	XIX	HCl
15I		608.3	16E	XIX	HCl
16I		615.3	17E	XIX	HCl

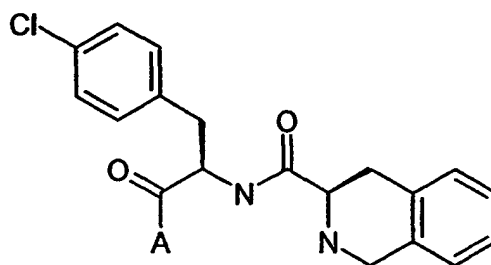
-163-

Example	A	ES MS (M + 1)	Starting From	Procedure	Salt Form
17I		553.3	18E	XIX	HCl
18I		551.3	19E	XIX	TFA
19I	 isomer 1	580.3	20E	XIX	HCl
20I	 isomer 2	580.3	20E	XIX	HCl
21I		600.4	1H	XIX	TFA

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Example	A	ES MS (M + 1)	Starting From	Procedure	Salt Form
22I		614.3	2H	XIX	TFA
23I		567.3	5H	XIX	TFA
24I		599	24D	XX	HCl

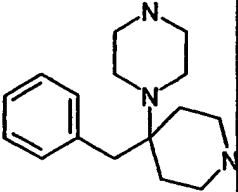
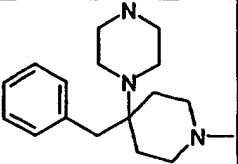
Compounds 1J and 2J were prepared from compounds of examples 5E and 3H respectively by using the procedure substantially similar to Procedure XIX. The hydrochloride salt can be prepared from the TFA salt by salt exchange in .5M HCl(aq) followed by lyophilization.



n*(salt form)

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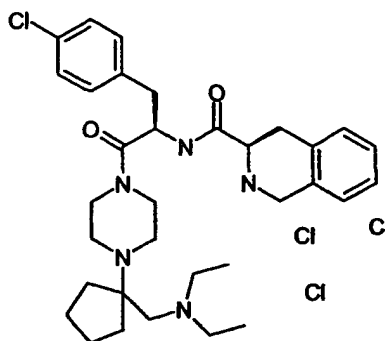
Table J

Example	A	ES MS (M + 1)	Starting From	Procedure	Salt Form
1J		600.3	5E	XIX	TFA
2J		614.3	3H	XIX	TFA

Procedure XXI

Example 1EE

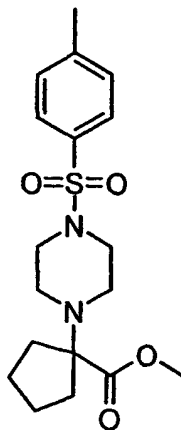
5



The compound of example 1EE was prepared using a procedure substantially similar to Procedure XX and starting materials originating from Preparations 1DD

10 (below) and BC1.

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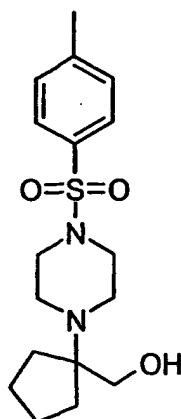
Preparation 1AA

Compound 1AA

To a mixture of cyclopentanone (8.9 mL, 100.5 mmol) and NH_4Cl (8.0 g, 150.8 mmol) at room temperature, a solution of KCN (9.8 g, 150.8 mmol) in H_2O (75 mL) was added and the mixture was vigorously stirred for two days. Reaction was then poured onto a 2:1 mixture of Et_2O and H_2O (150 mL) and aqueous layer extracted with Et_2O (3 x 50 mL). Combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to afford 1-amino-1-cyclopentanenitrile. This aminonitrile (2.0 g, 18.1 mmol) was dissolved in a saturated solution of HCl in methanol. To the resulting solution, H_2O (0.98 mL, 54.5 mmol) was added and mixture stirred at room temperature for one week. Solvent was evaporated under reduced pressure, residue taken into MeOH (100 mL) and stirred for 5 minutes. Solvent was removed under reduced pressure and solid residue washed with Et_2O to afford methyl 1-amino-1-cyclopentanecarboxylate hydrochloride. To a solution of methyl 1-amino-1-cyclopentanecarboxylate hydrochloride (3.2 g, 18.1 mmol) in anhydrous DMF (40 mL) and diisopropylethyl amine (100 mL), N,N -bis(2-chloroethyl)- p -toluenesulphonamide (5.9 g, 19.9 mmol) was added and reaction stirred under reflux (120°C) for 3 days. Solvent was removed under reduced pressure and residue taken into ethyl acetate (200 mL). Organic layer was washed with H_2O (2 x 50 mL) and brine, dried (Na_2SO_4), filtered and evaporated. Residue was purified by column chromatography (hexane-AcOEt 1:4) to afford the title compound (10% overall yield) as a white solid. MS m/z 367.2 ($\text{M}^+ + 1$).

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Procedure XXII

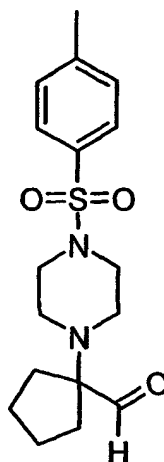
Preparation 1BB

Compound 1BB

- 5 To an ice cooled solution of compound 1AA (550 mg, 1.5 mmol) in anhydrous THF (15 mL) under nitrogen was added lithium aluminum hydride (120 mg, 3.15 mmol) portion wise. After 10 minutes, mixture was allowed to react at room temperature for 1 h and then carefully quenched with H₂O (0.10 mL) and 2N NaOH (0.4 mL) at 0°C. The mixture was stirred for 30 minutes and then filtered through Celite. Solvent was removed
- 10 under reduced pressure to afford the title compound (99%) as a white solid. MS m/z 339.2 (M⁺+1).

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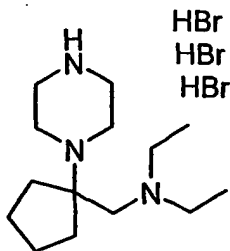
Procedure XXIII

Preparation 1CC

To a solution of oxalyl chloride (0.15 mL, 1.77 mmol) in anhydrous CH₂Cl₂ (15
5 mL) at -78°C under nitrogen atmosphere, DMSO (0.27 mL, 3.75 mmol) was added
dropwise and stirred for 30 minutes. To this mixture, a solution of the compound of
Preparation 1BB in CH₂Cl₂ (3 mL) was added dropwise and reaction was stirred at the
same temperature for 30 minutes. Then, Et₃N (1.05 mL, 7.5 mmol) was added and
mixture allowed to react at room temperature. After 30 minutes, the reaction was
10 quenched with H₂O, the layers were separated and the aqueous layer was extracted with
CH₂Cl₂ (2 X 10 mL). The combined organic layers were dried (Na₂SO₄), filtered and
evaporated to afford the title compound (99%). MS m/z 337.1 (M⁺+1).

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Procedure XXIV

Preparation 1DD

5

Compound 1DD

To a solution of Compound of preparation 1CC (450 mg, 1.34 mmol) and Et₂NH (0.15 mL, 1.47 mmol) in 1,2-dichloroethane (10 mL), sodium triacetoxyborohydride (400 mg, 1.9 mmol) was added in one portion. The mixture was stirred at room temperature for 3 days and then, additional Et₂NH (0.15 mL, 1.47 mmol) and sodium

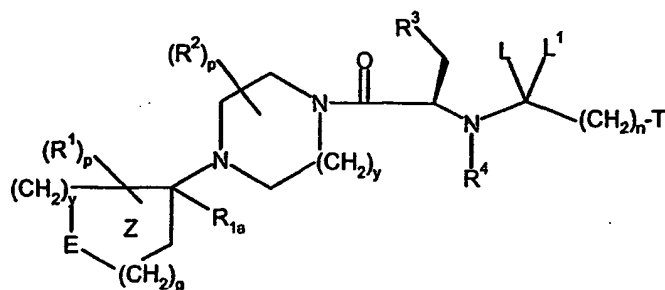
10 triacetoxyborohydride (400 mg, 1.9 mmol) were added. Reaction was stirred for 4 days and then quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. Combined organic layers were dried (Na₂SO₄), filtered and evaporated to give a residue that was purified by column chromatography (hexane-EtOAc 1:1, then EtOAc, then EtOAc -MeOH-Et₃N 90:5:5) to afford the *N*-tosyl protected compound as a pale yellow

15 oil. A solution of the *N*-tosyl derivative (220 mg, 0.56 mmol) in 30% HBr/AcOH (4.5 mL) was stirred at room temperature overnight. Solvent was evaporated under reduced pressure and solid residue washed with Et₂O to afford the title compound (38%) as a yellow solid. MS *m/z* 240.2 (M⁺+1)

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WHAT WE CLAIMS IS:

1. A compound of formula I:



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof,
wherein:

L and L¹ are both hydrogen or combine together to form an oxo group;

E is: O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹ may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

R¹ is selected from the group consisting of:

hydrogen,

C₁-C₈ alkyl,

C₂-C₈ alkenyl,

C₂-C₄ haloalkyl

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇

-171-

cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

R_{1a} is: hydrogen,

- 5 C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
(D)phenyl,
(D)aryl,
(D)heteroaryl;
10 (D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(CH₂)_mN(R⁸)₂,
(CH₂)_mNR⁸C(O)C₁-C₄ alkyl,
(CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),
15 (CH₂)_mOR⁸,
(CH₂)_mSC₁-C₄ alkyl,
(CH₂)_mSO(C₁-C₄ alkyl),
(CH₂)_mSO₂(C₁-C₄ alkyl), or
(CH₂)_mSO₂ N(R⁸)₂;

- 20 wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

25

R^{1b} is: hydrogen,

- C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
SO₂(C₁-C₈ alkyl),

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(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(D)CON(R⁸)₂, or
SO₂(D)phenyl, wherein the phenyl group is optionally substituted with one to five
5 substituent selected from halo, and C₁-C₈ alkyl;

R² is: hydrogen,
C₁-C₈ alkyl,
CONHC₁-C₄ alkyl,
10 (D)phenyl, oxo, or
(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring
carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;
15 wherein phenyl, aryl and thienyl are optionally substituted with one to three
substituents independently selected from the group consisting of:
cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄
alkoxy, C₁-C₄ haloalkyl;

20 R⁴ is: hydrogen,
C₁-C₈ alkyl,
CH₂(CH₂)_mC₁-C₄ alkoxy,
C(O)C₁-C₄ alkyl or
C(O)OC₁-C₄ alkyl;

25

R is: hydroxy,
halo,
C₁-C₈ alkyl,
C₂-C₈ alkenyl,

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- 5 C₁-C₈ alkoxy,
C₁-C₄ haloalkyl,
(D)C₃-C₇ cycloalkyl,
(D)aryl,
(D)heteroaryl;
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(D)C(O)heteroaryl,
(D)N(R⁸)₂,
10 (D)NR⁸C(O)C₁-C₄ alkyl,
(D)NR⁸SO₂(C₁-C₄ alkyl),
(D)OC₁-C₄ alkyl,
(D)OC(O)C₁-C₄ alkyl,
(D)heterocyclic,
15 (D)SC₁-C₄ alkyl, or
(D)SO₂N(R⁸)₂;
wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic,
and heteroaryl are optionally substituted with one to five substituents
independently selected from R⁸; and provided that when R is halo or hydroxy it is
20 not substituted on a carbon adjacent to a heteroatom;

each R⁸ is independently:

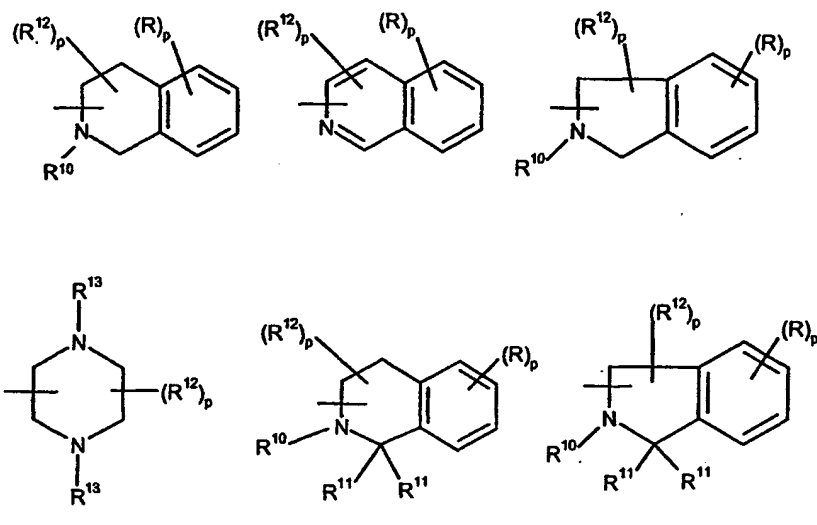
- hydrogen,
oxo,
25 C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
phenyl,
aryl or
heteroaryl,

-174-

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to three substituents selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are not substituted on a carbon adjacent to a heteroatom;

5

T is:



R⁹ is independently:

hydrogen,
 (C₁-C₈) alkyl,
 C₂-C₈ alkenyl,
 C(O)C₁-C₈ alkyl,
 C₂-C₈ alkynyl,
 phenyl,
 aryl, or
 heteroaryl;

R¹⁰ is: hydrogen,
 (C₁-C₈) alkyl,
 C₃-C₈ alkenyl,
 C(O)C₁-C₈ alkyl,

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C₂-C₈ alkynyl,
phenyl,
aryl, or
heteroaryl;

5

R¹¹ is independently:

hydrogen, (C₁-C₈) alkyl, (D)phenyl, or aryl;

R¹² is independently:

10

C₁-C₈ alkyl,
phenyl,
aryl,
heteroaryl,
(CH₂)_nN(R⁸)₂,

15

(CH₂)_nNR⁸C(O)C₁-C₄ alkyl,
(CH₂)_nNR⁸C(O)OC₁-C₄ alkyl,
(CH₂)_n(OCH₂CH₂)_qN(R⁸)₂,
(CH₂)_n(OCH₂CH₂)_qNR⁸C(O)C₁-C₄ alkyl,
(CH₂)_n(OCH₂CH₂)_qNR⁸SO₂(C₁-C₄ alkyl), or

20

(CH₂)_n[O]_q(C₁-C₈)alkylheterocyclic; and wherein for R¹², n is 2-8 when R¹² is substituted on a carbon atom adjacent to a heteroatom;

R¹³ is independently:

25

hydrogen,
C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
(D)phenyl,
C(O)C₁-C₈ alkyl,
SO₂C₁-C₈ alkyl, or

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SO₂-phenyl;D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

5 y is: 1 or 2;

m is: 1-4;

n is: 0-8;

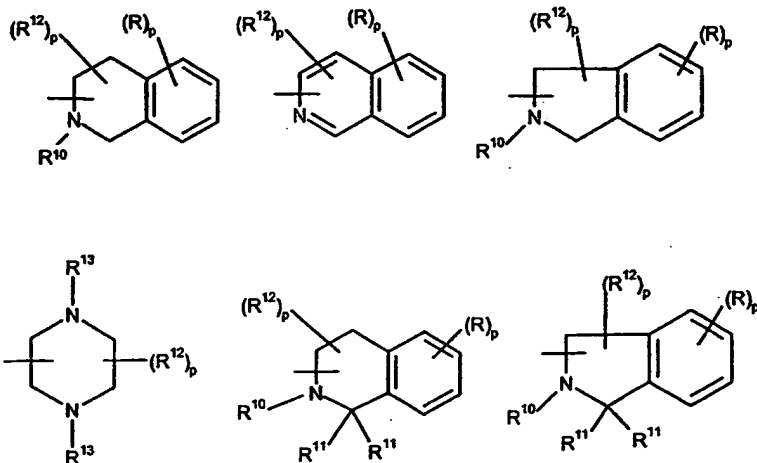
p is: 0-4; and

q is: 0-1.

- 10 2. The compound according to Claim 1 wherein for the Z ring y is 1, or 2.
3. The compound according to Claim 1 wherein the Z ring is saturated.
4. The compound according to Claim 1 wherein the Z ring is cyclopentyl or cyclohexyl.
5. The compound according to Claim 3 wherein E is O, S, NR^{1b}, SO₂, SO, or
- 15 CHR⁹.
6. The compound according to Claim 1 wherein E is CH₂.
7. The compound according to Claim 1 wherein E is CHR⁹ and R⁹ combines with adjacent R¹ to form a benzene ring.
8. The compound according to Claim 1 wherein for the Z ring R¹ is
- 20 hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₂-C₄ haloalkyl, (D)C₃-C₇ cycloalkyl, 2-fluorobenzyl, (D)phenyl, (CH₂)_mC(O)C₁-C₄ alkyl, (CH₂)_mN(R⁸)₂, or (CH₂)_mNR⁸C(O)C₁-C₄ alkyl; D is a bond or CH₂; and p is 1; and m is 1.
9. The compound according to Claim 1 wherein R is hydrogen, methyl, trifluoromethyl, phenyl or benzyl, wherein phenyl and benzyl groups are optionally
- 25 substituted with halo or hydroxy and p is 1.
10. The compound according to Claim 1 wherein R^{1a} is C₁-C₈ alkyl, C₁-C₈ alkenyl, C₂-C₄ haloalkyl, (D)C₃-C₇ cycloalkyl, (D)phenyl, (D)COR⁸, (D)N(R⁸)₂, or (D)NR⁸COR⁸.

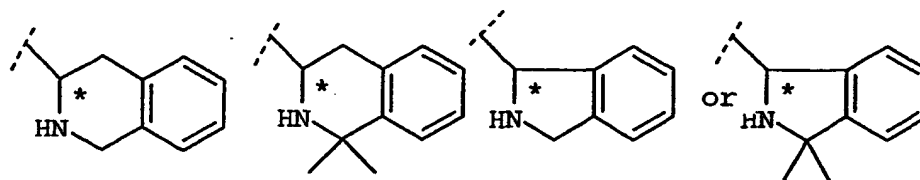
-177-

11. The compound according to Claim 1 wherein R^{1a} is isopropyl, isobutyl, cyclohexylmethyl, phenyl, 2-fluorobenzyl or benzyl.
12. The compound according to Claim 11 wherein E is selected from the group consisting of: $-NCH_3$, $-NCH(CH_3)_2$, S, CR^9 , $C(R^9)_2$, $-NC(O)CH_3$, -
- 5 $NC(O)CH(CH_3)_2$, $-NCH_2CH_3$, NSO_2CH_3 , and O.
13. The compound according to Claim 12 wherein E is CR^9 or $C(R^9)_2$, wherein each R^9 is independently selected from hydrogen and C_1 - C_4 alkyl, and wherein each R^9 may combine with an adjacent R^1 to form a 5 or 6-member carbocycle.
14. The compound according to Claim 1 wherein R^2 is hydrogen, C_1 - C_8 alkyl,
- 10 C_1 - C_4 haloalkyl, (D) C_3 - C_7 cycloalkyl, (D)phenyl, or (D) $C(O)C_1$ - C_8 alkyl.
15. The compound of Claim 1 wherein R^3 is phenyl optionally being para-substituted with chloro, bromo, benzyloxy, methoxy or methyl.
16. The compound of any one of Claims 1 to 15 wherein R^3 is phenyl para-substituted with chloro.
- 15 17. The compound of any one of Claims 1 to 15 wherein R^{10} is hydrogen, C_1 - C_4 alkyl, or $C(O)C_1$ - C_4 alkyl.
18. The compound of any one of Claims 1 to 15 wherein R^{10} is hydrogen at each occurrence.
19. The compound of any one of Claims 1-15 wherein T of the C domain is
- 20 selected from the group consisting of:

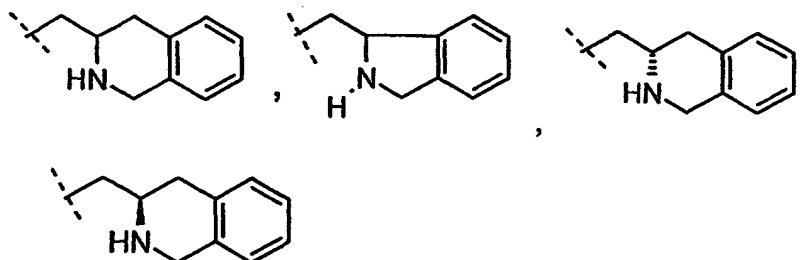


-178-

20. The compound according to Claims 1 to 15 wherein "T" is a moiety of the formula:

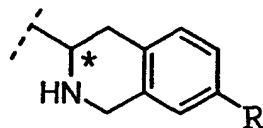


21. The compound according to any of Claims 1 to 15 wherein "T" is a moiety
5 selected from the group consisting of:



and

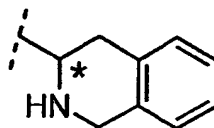
22. The compound of any one of Claims 1 to 15 wherein T is a moiety of the formula:



10

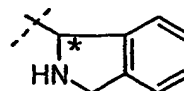
wherein R is as described; and wherein the carbon atom marked * represents a chiral center.

23. The compound of any one of Claims 1 to 15 wherein L and L¹ are each hydrogen; and T is a moiety of the formula:



15

24. The compound according to any one of Claims 1 to 15 wherein L and L¹

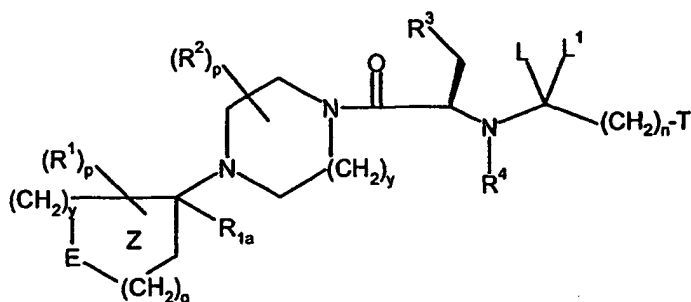


are each hydrogen, and T is a moiety of the formula:

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25. The compound of Claim 22, 23, or 24 wherein the carbon atom marked with * has the R or S configuration.

26. Use of a compound of formula I:



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof,
wherein:

L and L¹ are both hydrogen or combine together to form an oxo group;

10 E is: O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹ may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

15 R¹ is selected from the group consisting of:

Hydrogen,

C₁-C₈ alkyl,

C₂-C₈ alkenyl,

C₂-C₄ haloalkyl

20 (D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted

25 with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇

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cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

R_{1a} is: hydrogen,

- 5 C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
(D)phenyl,
(D)aryl,
(D)heteroaryl;
10 (D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(CH₂)_mN(R⁸)₂,
(CH₂)_mNR⁸C(O)C₁-C₄ alkyl,
(CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),
15 (CH₂)_mOR⁸,
(CH₂)_mSC₁-C₄ alkyl,
(CH₂)_mSO(C₁-C₄ alkyl),
(CH₂)_mSO₂(C₁-C₄ alkyl), or
(CH₂)_mSO₂ N(R⁸)₂;

- 20 wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

25

R^{1b} is: hydrogen,

- C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
SO₂(C₁-C₈ alkyl),

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(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(D)CON(R⁸)₂, or
SO₂(D)phenyl, wherein the phenyl group is optionally substituted with one to five
5 substituents selected from halo, and C₁-C₈ alkyl;

R² is: hydrogen,
C₁-C₈ alkyl,
CONHC₁-C₄ alkyl,
10 (D)phenyl, oxo, or
(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring
carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;
15 wherein phenyl, aryl and thienyl are optionally substituted with one to three
substituents independently selected from the group consisting of:
cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄
alkoxy, C₁-C₄ haloalkyl;

20 R⁴ is: hydrogen,
C₁-C₈ alkyl,
CH₂(CH₂)_mC₁-C₄ alkoxy,
C(O)C₁-C₄ alkyl, or
C(O)OC₁-C₄ alkyl;

25 R is: hydroxy,
halo,
C₁-C₈ alkyl,
C₂-C₈ alkenyl,

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- 5 C₁-C₈ alkoxy,
C₁-C₄ haloalkyl,
(D)C₃-C₇ cycloalkyl,
(D)aryl,
(D)heteroaryl;
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(D)C(O)heteroaryl,
(D)N(R⁸)₂,
10 (D)NR⁸C(O)C₁-C₄ alkyl,
(D)NR⁸SO₂(C₁-C₄ alkyl),
(D)OC₁-C₄ alkyl,
(D)OC(O)C₁-C₄ alkyl,
(D)heterocyclic,
15 (D)SC₁-C₄ alkyl, or
(D)SO₂N(R⁸)₂;
wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic,
and heteroaryl are optionally substituted with one to five substituents
independently selected from R⁸; and provided that when R is halo or hydroxy it is
20 not substituted on a carbon adjacent to a heteroatom;

each R⁸ is independently:

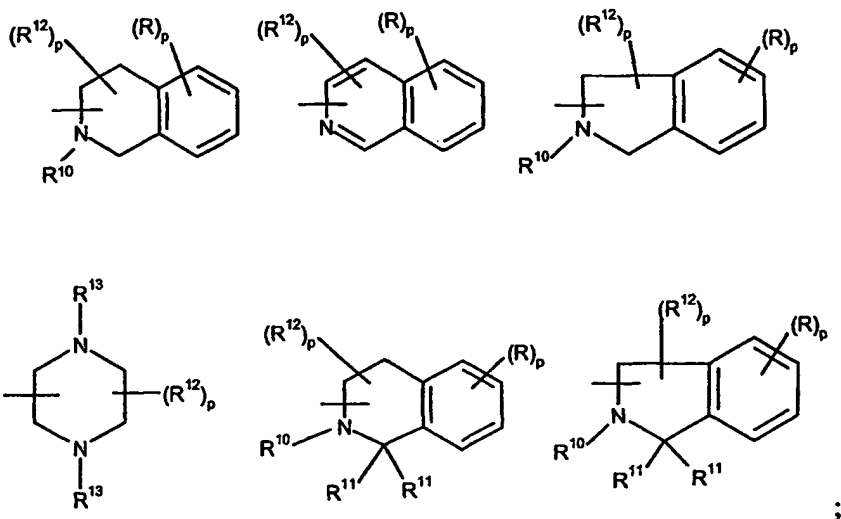
- hydrogen,
oxo,
25 C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
phenyl,
aryl or
heteroaryl,

-183-

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to three substituents selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are not substituted on a carbon adjacent to a heteroatom;

5

T is:



R^9 is independently:

- 10 hydrogen,
 (C₁-C₈) alkyl,
 C₂-C₈ alkenyl,
 C(O)C₁-C₈ alkyl,
 C₂-C₈ alkynyl,
 15 phenyl,
 aryl, or
 heteroaryl;

R^{10} is: hydrogen,

- 20 (C₁-C₈) alkyl,
 C₃-C₈ alkenyl,

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C(O)C₁-C₈ alkyl,C₂-C₈ alkynyl,

phenyl,

aryl, or

5 heteroaryl;

R¹¹ is independently:hydrogen, (C₁-C₈) alkyl, (D)phenyl, or aryl;R¹² is independently:10 C₁-C₈ alkyl,

phenyl,

aryl,

heteroaryl,

(CH₂)_nN(R⁸)₂,15 (CH₂)_nNR⁸C(O)C₁-C₄ alkyl,(CH₂)_nNR⁸C(O)OC₁-C₄ alkyl,(CH₂)_n(OCH₂CH₂)_qN(R⁸)₂,(CH₂)_n(OCH₂CH₂)_qNR⁸C(O)C₁-C₄ alkyl,(CH₂)_n(OCH₂CH₂)_qNR⁸SO₂(C₁-C₄ alkyl), or20 (CH₂)_n[O]_q(C₁-C₈)alkylheterocyclic; and wherein for R¹², n is 2-8 when R¹² is substituted on a carbon atom adjacent to a heteroatom;R¹³ is independently:

hydrogen,

25 C₁-C₈ alkyl,(D)C₃-C₇ cycloalkyl,

(D)phenyl,

C(O) C₁-C₈ alkyl,SO₂C₁-C₈ alkyl, or

-185-

SO₂-phenyl;D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

y is: 1 or 2;

5 m is: 1-4;

n is: 0-8;

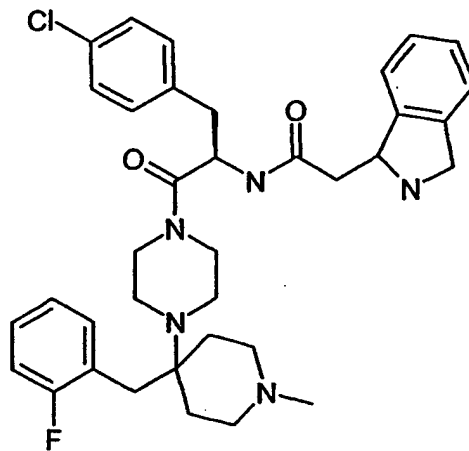
p is: 0-4; and

q is: 0-1, in the manufacture of a medicament for treating obesity and/or diabetes.

27. A pharmaceutical composition comprising a compound of any one of
 10 Claims 1-25 and a pharmaceutical carrier.

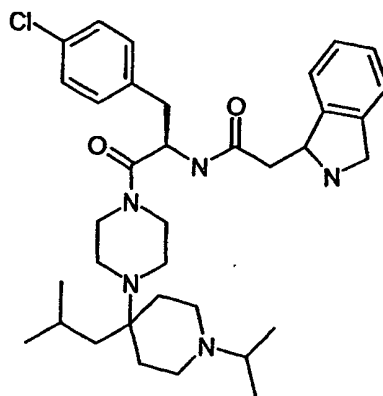
28. The pharmaceutical composition of Claim 27 further comprising a second
 active ingredient selected from the group consisting of an insulin sensitizer, insulin
 mimetic, sulfonylurea, alpha-glucosidase inhibitor, HMG-CoA reductase inhibitor,
 sequestrant cholesterol lowering agent, beta 3 adrenergic receptor agonist, neuropeptide Y
 15 antagonist, phosphodiester V inhibitor, and an alpha2 adrenergic receptor antagonist.

29. A compound selected from the group consisting of:

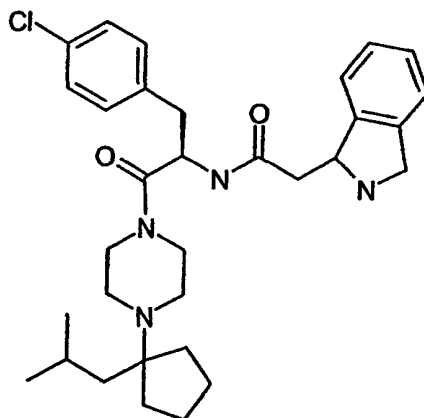


N-(1-(4-Chloro-benzyl)-2-{4-[4-(2-fluoro-benzyl)-1-methyl-piperidin-4-yl]-piperazin-1-yl}-2-oxo-ethyl)-2-(2,3-dihydro-1H-indol-1-yl)-acetamide,

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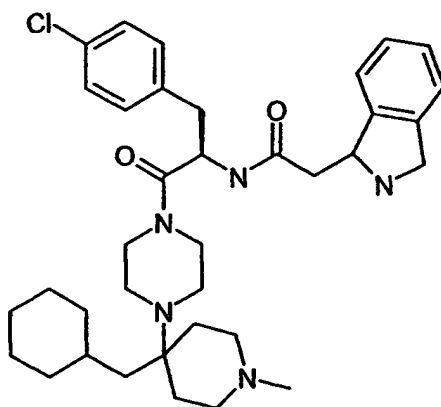
N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1-isopropyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



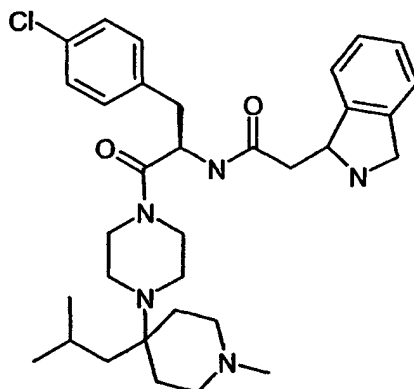
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N-{1-(4-Chloro-benzyl)-2-[4-(1-isobutyl-cyclopentyl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

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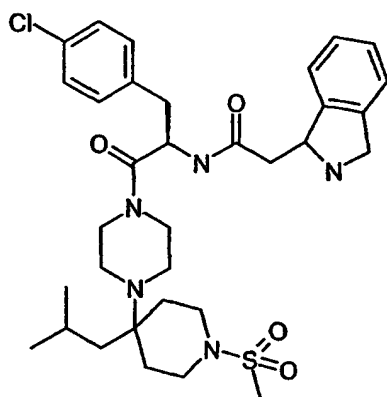
N-{1-(4-Chloro-benzyl)-2-[4-(4-cyclohexylmethyl-1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



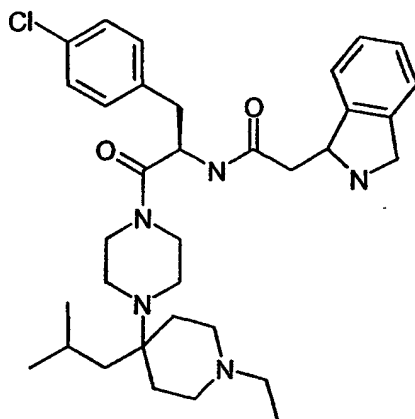
5

N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-188-



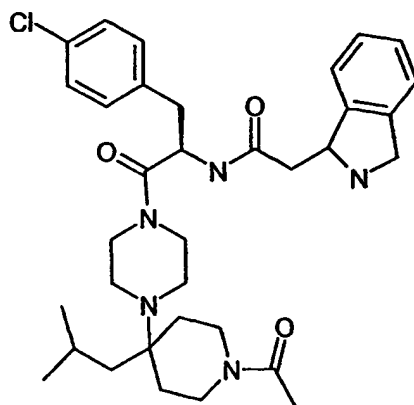
N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1-methanesulfonyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



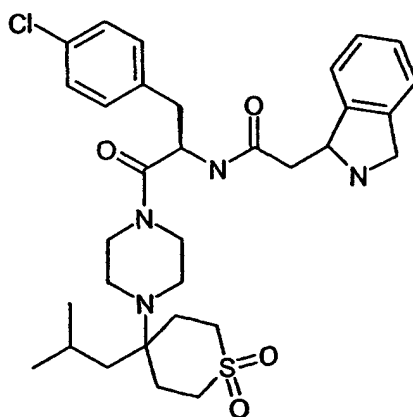
5

N-{1-(4-Chloro-benzyl)-2-[4-(1-ethyl-4-isobutyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-189-



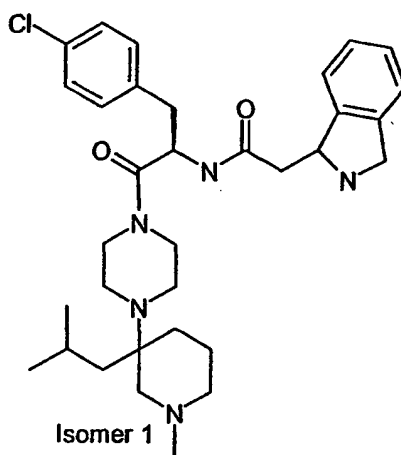
N-[2-[4-(1-Acetyl-4-isobutyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-chloro-benzyl)-2-oxo-ethyl]-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,



5

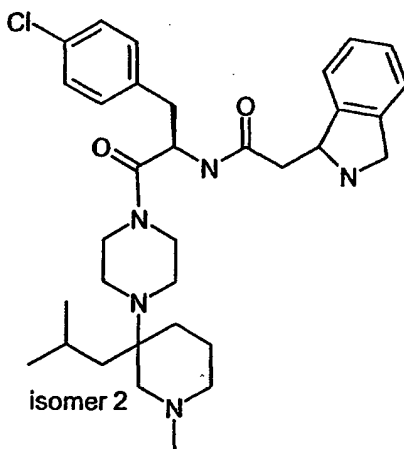
N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-190-



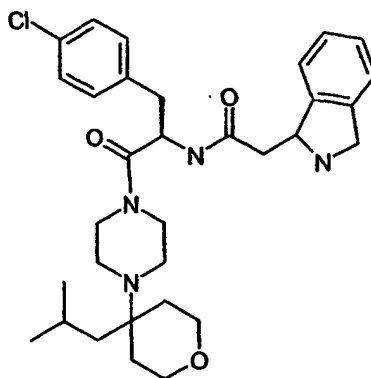
N-{1-(4-Chloro-benzyl)-2-[4-(3-isobutyl-1-methyl-piperidin-3-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

5

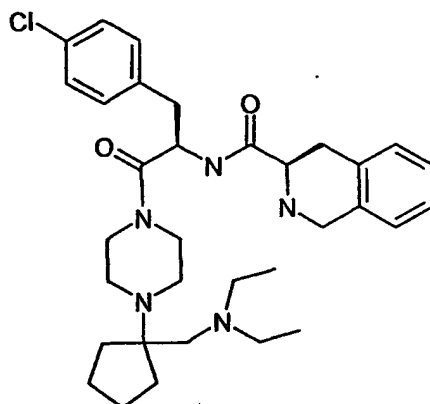


N-{1-(4-Chloro-benzyl)-2-[4-(3-isobutyl-1-methyl-piperidin-3-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide,

-191-



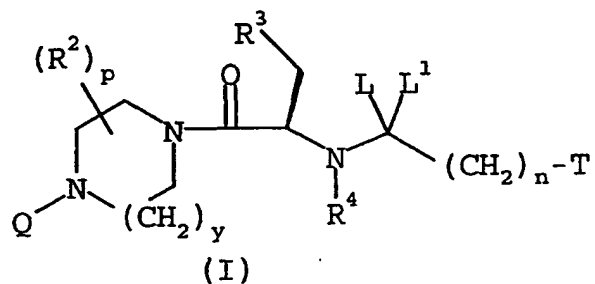
N-{1-(4-Chloro-benzyl)-2-[4-(4-isobutyl-tetrahydro-pyran-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-2-(2,3-dihydro-1H-isoindol-1-yl)-acetamide, and



5

1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {1-(4-chloro-benzyl)-2-[4-(1-diethylaminomethyl-cyclopentyl)-piperazin-1-yl]-2-oxo-ethyl}-amide, and its pharmaceutically acceptable salt, solvate, prodrug and enantiomer thereof.

30. A process for preparing a compound of formula I:



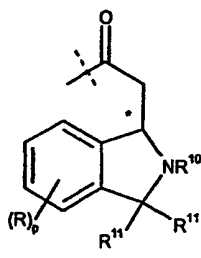
10

or a pharmaceutically acceptable salt or stereoisomer thereof,

-192-

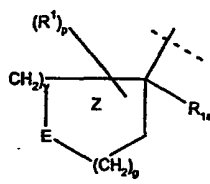
wherein:

-CLL'-(CH₂)_n-T is:



R¹⁰ is a CBz or Boc protecting group, hydrogen, (C₁-C₈) alkyl, C₃-C₈ alkenyl, C(O)C₁-
 5 C₈ alkyl, C₂-C₈ alkynyl, phenyl, aryl, or heteroaryl;

Q is represent the moiety:



L and L¹ are both hydrogen or combine together to form an oxo group;
 10

E is: O, S, NR^{1b}, SO, SO₂, CR⁹, or C(R⁹)₂, provided that when E is CR⁹, or C(R⁹)₂, R⁹
 may combine with an adjacent R¹ to form a 5, 6, or 7-member saturated or unsaturated
 carbocycle;

wherein the Z ring has 0, or 1 double bond;

15

R¹ is selected from the group consisting of:

hydrogen,

C₁-C₈ alkyl,

C₂-C₈ alkenyl,

20 C₂-C₄ haloalkyl

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

-193-

C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇ cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

R_{1a} is: hydrogen,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

(D)phenyl,

(D)aryl,

(D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,

(D)C(O)OC₁-C₄ alkyl,

(CH₂)_mN(R⁸)₂,

(CH₂)_mNR⁸C(O)C₁-C₄ alkyl,

(CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),

(CH₂)_mOR⁸,

(CH₂)_mSC₁-C₄ alkyl,

(CH₂)_mSO(C₁-C₄ alkyl),

(CH₂)_mSO₂(C₁-C₄ alkyl), or

(CH₂)_mSO₂ N(R⁸)₂;

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

R^{1b} is: hydrogen,

C₁-C₈ alkyl,

-194-

(D)C₃-C₇ cycloalkyl,
SO₂(C₁-C₈ alkyl),
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
5 (D)CON(R⁸)₂, or
SO₂(D)phenyl, wherein the phenyl group is optionally substituted with one to five
substituents selected from halo, and C₁-C₈ alkyl;

R² is: hydrogen,
10 C₁-C₈ alkyl,
CONHC₁-C₄ alkyl,
(D)phenyl,
oxo, or
(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring
15 carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;
wherein phenyl, aryl and thienyl are optionally substituted with one to three
substituents independently selected from the group consisting of:
20 cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄
alkoxy, C₁-C₄ haloalkyl;

R⁴ is: hydrogen,
C₁-C₈ alkyl,
25 CH₂(CH₂)_mC₁-C₄ alkoxy,
C(O)C₁-C₄ alkyl, or
C(O)OC₁-C₄ alkyl;

R is: hydroxy,
halo,

-195-

- 5 C₁-C₈ alkyl,
C₂-C₈ alkenyl,
C₁-C₈ alkoxy,
C₁-C₄ haloalkyl,
(D)C₃-C₇ cycloalkyl,
(D)aryl,
(D)heteroaryl;
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
10 (D)C(O)heteroaryl,
(D)N(R⁸)₂,
(D)NR⁸C(O)C₁-C₄ alkyl,
(D)NR⁸SO₂(C₁-C₄ alkyl),
(D)OC₁-C₄ alkyl,
15 (D)OC(O)C₁-C₄ alkyl,
(D)heterocyclic,
(D)SC₁-C₄ alkyl, or
(D)SO₂N(R⁸)₂;
wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic,
20 and heteroaryl are optionally substituted with one to five substituents
independently selected from R⁸; and provided that when R is halo or hydroxy it is
not substituted on a carbon adjacent to a heteroatom;

- each R⁸ is independently:
25 hydrogen,
oxo,
C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,

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phenyl,

aryl or

heteroaryl,

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally

5 substituted with one to three substituents selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are not substituted on a carbon adjacent to a heteroatom;

R⁹ is independently hydrogen, (C₁-C₈) alkyl, C₂-C₈ alkenyl, C(O)C₁-C₈ alkyl, C₂-C₈ alkynyl, phenyl, aryl, or heteroaryl;

10

R¹¹ is independently:hydrogen, (C₁-C₈) alkyl, (D)phenyl or aryl;D is: a bond or C₁-C₄ alkyl;

15 g is: 0, 1, or 2;

y is: 1 or 2;

m is: 1-4;

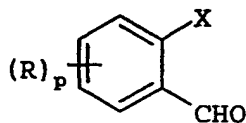
n is: 0-8;

p is: 0-4; and

20 q is: 0-1;

comprising the steps of:

b) reacting a compound having a structural formula 1:

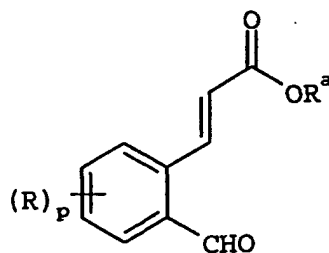


(1)

25

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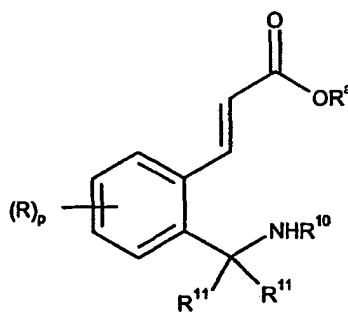
with $\text{CH}_2\text{CH}=\text{C}(\text{O})\text{OR}^a$ wherein R^a is hydrogen or $\text{C}_1\text{-C}_8$ alkyl and X is halo, in the presence of a catalyst and a base in a suitable organic solvent to give the compound of formula 2:



5

(2);

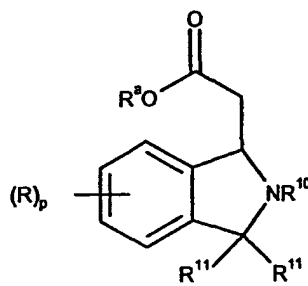
f) reductively aminating the compound of formula 2 in the presence of amine in an acidic condition to give a compound of formula 3:



10

(3);

g) cyclizing the compound of formula 3 by Michael addition to give a compound of formula 4 or stereoisomers thereof:

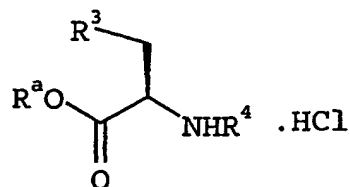


15

(4);

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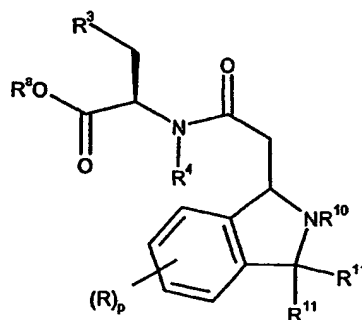
h) coupling the compound of formula 4 or stereoisomers thereof wherein R^a is H, with a compound of formula 5:



(5);

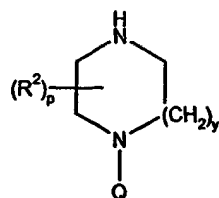
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wherein R^a is C₁-C₈ alkyl, to give a compound of formula 6:



(6); and

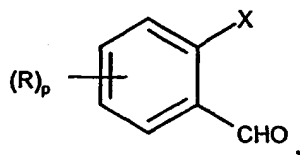
10 i) coupling the compound of formula 6 wherein R^a is H, with a compound having a structural formula:



to afford the compound of formula 1.

31. The process of Claim 30, wherein:

15



in Step a) is 2-bromobenzaldehyde.

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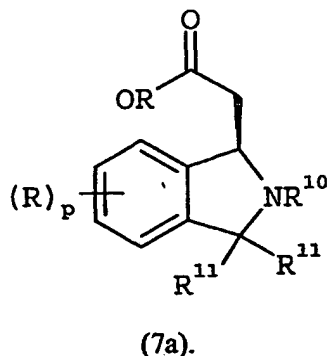
32. The process of Claim 31, wherein $\text{CH}_2\text{CH}=\text{C}(\text{O})\text{OR}^a$ in Step (a) is methylacrylate.

33. The process of Claim 32, wherein the catalyst in Step (a) is selected from the group consisting of: $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$, $\text{Pd}(\text{Ph}_3\text{P})_4\text{Cl}_2$, $\text{Pd}(\text{Ph}_3\text{P})_4$, $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2/\text{CuI}$,
 5 $\text{Pd}(\text{OAc})_2/\text{Ph}_3\text{P}-\text{Bu}_4\text{NBr}$, $\text{Pd}(\text{Ph}_3\text{P})_4\text{Cl}_2/\text{H}_2$ and $\text{Pd}(\text{OAc})_2/\text{P}(\text{O}-\text{tol})_3$; and wherein the base in Step (a) is $\text{N}(\text{R})_3$ where R is hydrogen or $\text{C}_1\text{-C}_8$ alkyl.

34. The process of Claim 33, wherein the amine in Step (b) is selected from the group consisting of: benzylamine, alpha-methylbenzylamine and BocNH_2 .

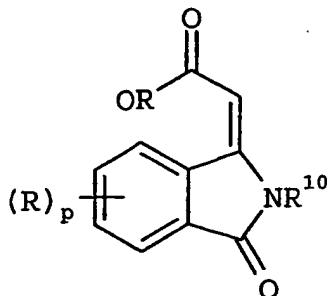
35. The process of Claim 34, wherein Step (b) further comprises the step of
 10 reducing an intermediate imine compound in the presence of reducing agent selected from the group consisting of: NaCNBH_3 , $\text{Na}(\text{OAc})_3\text{BH}$, NaBH_4/H^+ and a combination of Et_3SiH and TFA in CH_3CN or CH_2Cl_2 .

36. The process of Claim 31, wherein the stereoisomer of compound of formula (7) in Step (c) is a compound of formula 7a:



15

37. The process of Claim 36, wherein the compound of formula 7a is prepared by asymmetric hydrogenation of a compound having structural formula,



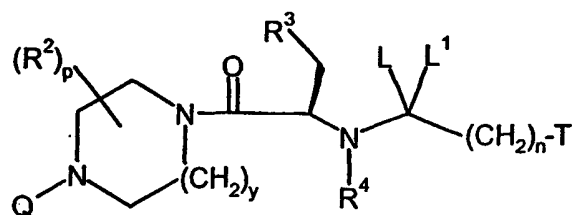
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-200-

38. The process of Claim 31, wherein the Michael addition in Step (c) is carried out under basic workup condition.

39. The process of Claim 31, wherein the Step (e) further comprises deprotecting or protecting of the compound of formula (4) at NR^{10} .

5 40. A process for preparing a compound of formula I:

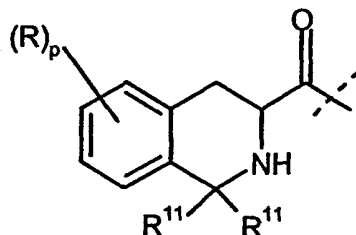


(I)

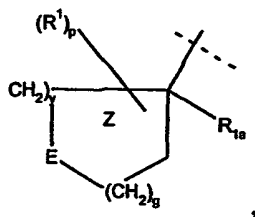
or a pharmaceutically acceptable salt or stereoisomer thereof,

10 wherein:

— $\text{LL}'(\text{CH}_2)_n\text{-T}$ is represented by the group:



and Q represents the moiety:



15

E is: O , S , NR^{1b} , SO , SO_2 , CR^9 , or $\text{C}(\text{R}^9)_2$, provided that when E is CR^9 , or $\text{C}(\text{R}^9)_2$, R^9 may combine with an adjacent R^1 to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

20

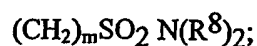
-201-

R¹ is selected from the group consisting of:

- hydrogen,
C₁-C₈ alkyl,
C₂-C₈ alkenyl,
5 C₂-C₄ haloalkyl
(D)C₃-C₇ cycloalkyl,
(D)phenyl,
aryl,
C(O)OC₁-C₈ alkyl,
10 wherein phenyl, aryl, alkenyl, and cycloalkyl groups are optionally substituted
with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇
cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom
adjacent to a heteroatom;

- 15 R_{1a} is: hydrogen,
C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
(D)phenyl,
(D)aryl,
20 (D)heteroaryl;
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(CH₂)_mN(R⁸)₂,
(CH₂)_mNR⁸C(O)C₁-C₄ alkyl,
25 (CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),
(CH₂)_mOR⁸,
(CH₂)_mSC₁-C₄ alkyl,
(CH₂)_mSO(C₁-C₄ alkyl),
(CH₂)_mSO₂(C₁-C₄ alkyl), or

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wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy, and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

R^{1b} is: hydrogen,

C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
SO₂(C₁-C₈ alkyl),
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
(D)CON(R⁸)₂, or
SO₂(D)phenyl, wherein the phenyl group is optionally substituted with one to five substituent selected from halo, and C₁-C₈ alkyl;

R² is: hydrogen,

C₁-C₈ alkyl,
CONHC₁-C₄ alkyl,
(D)phenyl,
oxo, or
(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

R³ is: phenyl, aryl or thienyl;

wherein phenyl, aryl and thienyl are optionally substituted with one to three substituents independently selected from the group consisting of:

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cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl;

- R⁴ is: hydrogen,
5 C₁-C₈ alkyl,
CH₂(CH₂)_mC₁-C₄ alkoxy,
C(O)C₁-C₄ alkyl or
C(O)OC₁-C₄ alkyl;
- 10 R is: hydroxy,
halo,
C₁-C₈ alkyl,
C₂-C₈ alkenyl,
C₁-C₈ alkoxy,
15 C₁-C₄ haloalkyl,
(D)C₃-C₇ cycloalkyl,
(D)aryl,
(D)heteroaryl;
(D)C(O)C₁-C₄ alkyl,
20 (D)C(O)OC₁-C₄ alkyl,
(D)C(O)heteroaryl,
(D)N(R⁸)₂,
(D)NR⁸C(O)C₁-C₄ alkyl,
(D)NR⁸SO₂(C₁-C₄ alkyl),
25 (D)OC₁-C₄ alkyl,
(D)OC(O)C₁-C₄ alkyl,
(D)heterocyclic,
(D)SC₁-C₄ alkyl, or

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(D)SO₂N(R⁸)₂;

wherein C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, phenyl, aryl, heterocyclic, and heteroaryl are optionally substituted with one to five substituents

independently selected from R⁸; and provided that when R is halo or hydroxy it is not substituted on a carbon adjacent to a heteroatom;

each R⁸ is independently:

hydrogen,

oxo,

C₁-C₈ alkyl,

(D)C₃-C₇ cycloalkyl,

phenyl,

aryl or

heteroaryl,

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to three substituents selected from the group consisting of C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are not substituted on a carbon adjacent to a heteroatom;

R⁹ is independently:

hydrogen,

(C₁-C₈) alkyl,

C₂-C₈ alkenyl,

C(O)C₁-C₈ alkyl,

C₂-C₈ alkynyl,

phenyl,

aryl, or

heteroaryl;

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R^{10} is: hydrogen,
 (C₁-C₈) alkyl,
 C₃-C₈ alkenyl,
 C(O)C₁-C₈ alkyl,
 5 C₂-C₈ alkynyl,
 phenyl,
 aryl, or
 heteroaryl;

10 R^{11} is independently:
 hydrogen, (C₁-C₈) alkyl, or (D)phenyl, or aryl;

D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

15 y is: 1 or 2;

m is: 1-4;

n is: 0-8;

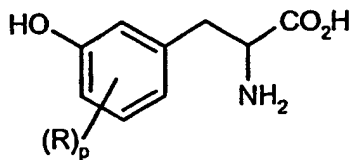
p is: 0-4; and

q is: 0-1;

20

comprising the steps of:

b) esterifying a compound of formula 1 with an alcohol R^aOH

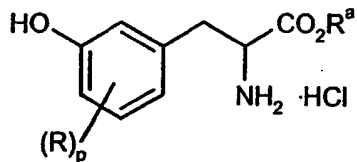


1;

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-206-

to form a compound of formula 2:



2;

wherein R^a is a group selected from C_1 - C_4 alkyl, and (D) phenyl;

5

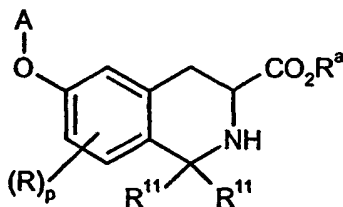
i) reacting a compound of formula 2 with $R^{11}COR^{11}$ to form a compound of formula:



3;

10 wherein R^{11} is independently hydrogen, C_1 - C_4 alkyl;

j) reacting a compound of formula 3 with an activating group to form a compound of formula 4:



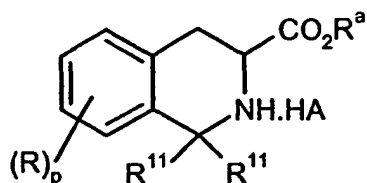
4;

15

wherein A is an activating group;

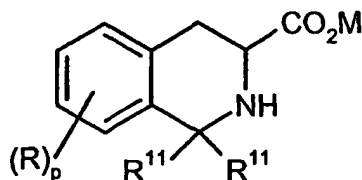
-207-

k) deoxygenating the compound of formula 4 by hydrogenation to afford a compound of formula 5:



5;

5 l) optionally reacting the compound of formula 5 wherein HA is an acidic, with an inorganic base to form a compound of formula 6:

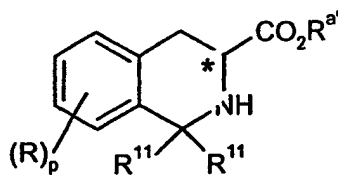


6;

wherein M is a univalent cation;

10

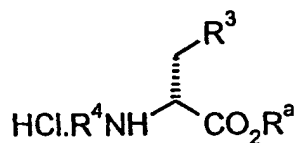
m) resolving the compound of formula 5 or the compound of formula 6 wherein M is hydrogen to afford a chiral compound of formula 7:



7;

15 wherein Ra' is H or R^a;

n) coupling the compound of formula 7 with a compound of formula 8:

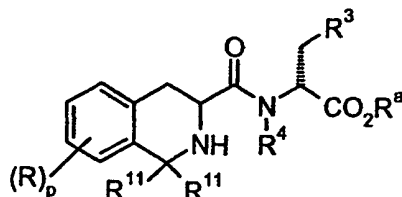


8;

20

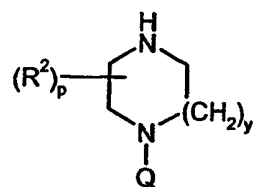
-208-

to afford a compound of formula 9:



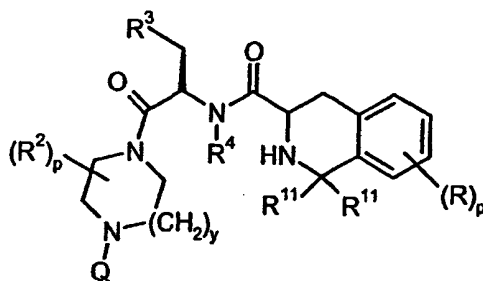
9.

- 5 o) coupling the compound of formula 9 with a compound of formula 10:



10;

to afford a compound of formula I:

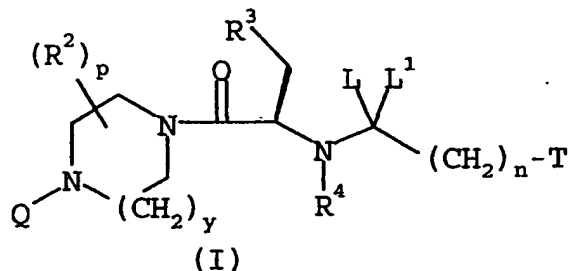


I.

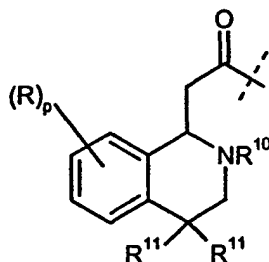
41. The process according to Claim 40 wherein the esterification is performed via an acylhalide intermediate formed by reaction of compound (1) with thionyl chloride, or oxalylchloride.
- 15 42. The process according to Claim 41 wherein the activating agent is trifluoromethanesulfonic anhydride to form the triflate.

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43. A process for preparing a compound of formula I:



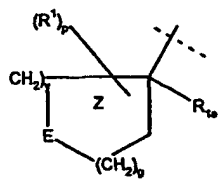
or a pharmaceutically acceptable salt or stereoisomer thereof,
wherein $-LL'(CH_2)_n-T$ is represented by the group:



5

R^{10} is a CBz or Boc protecting group, hydrogen, (C_1-C_8) alkyl, C_3-C_8 alkenyl, $C(O)C_1-C_8$ alkyl, C_2-C_8 alkynyl, phenyl, aryl, or heteroaryl;

Q represents the moiety:



10

E is: O, S, NR^{1b} , SO, SO_2 , CR^9 , or $C(R^9)_2$, provided that when E is CR^9 , or $C(R^9)_2$, R^9 may combine with an adjacent R^1 to form a 5, 6, or 7-member saturated or unsaturated carbocycle;

wherein the Z ring has 0, or 1 double bond;

15

R^1 is selected from the group consisting of:

hydrogen,
 C_1-C_8 alkyl,
 C_2-C_8 alkenyl,

-210-

C₂-C₄ haloalkyl(D)C₃-C₇ cycloalkyl,

(D)phenyl,

aryl,

5 C(O)OC₁-C₈ alkyl,

wherein phenyl, aryl alkenyl, and cycloalkyl groups are optionally substituted with hydroxy, halo, C₁-C₈ alkyl, C₁-C₄ alkoxy, C₂-C₄ haloalkyl, and (D)C₃-C₇ cycloalkyl provided that the halo, hydroxy are not substituted on a carbon atom adjacent to a heteroatom;

10

R_{1a} is: hydrogen,C₁-C₈ alkyl,(D)C₃-C₇ cycloalkyl,

(D)phenyl,

15

(D)aryl,

(D)heteroaryl;

(D)C(O)C₁-C₄ alkyl,(D)C(O)OC₁-C₄ alkyl,(CH₂)_mN(R⁸)₂,

20

(CH₂)_mNR⁸C(O)C₁-C₄ alkyl,(CH₂)_mNR⁸SO₂(C₁-C₄ alkyl),(CH₂)_mOR⁸,(CH₂)_mSC₁-C₄ alkyl,(CH₂)_mSO(C₁-C₄ alkyl),

25

(CH₂)_mSO₂(C₁-C₄ alkyl), or(CH₂)_mSO₂ N(R⁸)₂;

wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of perfluoroC₁-C₄ alkoxy, halo, hydroxy, C₁-C₈ alkyl, C₁-C₄ alkoxy,

-211-

and C₁-C₄ haloalkyl; provided that halo and hydroxy groups are not substituted on a carbon atom adjacent to a heteroatom;

R^{1b} is: hydrogen,

- 5 C₁-C₈ alkyl,
(D)C₃-C₇ cycloalkyl,
SO₂(C₁-C₈ alkyl),
(D)C(O)C₁-C₄ alkyl,
(D)C(O)OC₁-C₄ alkyl,
10 (D)CON(R⁸)₂, or
SO₂(D)phenyl, wherein the phenyl group is optionally substituted with one to 1 to 5 substituent selected from halo, and C₁-C₈ alkyl;

R² is: hydrogen,

- 15 C₁-C₈ alkyl,
CONHC₁-C₄ alkyl,
(D)phenyl, oxo, or
(D)C₃-C₇ cycloalkyl, provided that when R² is oxo, R² is on one of the ring carbon atoms adjacent to the nitrogen atom bearing the Z ring;

20

R³ is: phenyl, aryl or thienyl;

- wherein phenyl, aryl and thienyl are optionally substituted with one to three substituents independently selected from the group consisting of:
cyano, perfluoroC₁-C₄ alkoxy, halo, C₁-C₈ alkyl, (D)C₃-C₇ cycloalkyl, C₁-C₄
25 alkoxy, C₁-C₄ haloalkyl;

R⁴ is: hydrogen,

- C₁-C₈ alkyl,
CH₂(CH₂)_mC₁-C₄ alkoxy,

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 $C(O)C_1-C_4$ alkyl, or $C(O)OC_1-C_4$ alkyl;

R is: hydroxy,

5 halo,

 C_1-C_8 alkyl, C_2-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_4 haloalkyl,10 (D) C_3-C_7 cycloalkyl,

(D)aryl,

(D)heteroaryl;

(D) $C(O)C_1-C_4$ alkyl,(D) $C(O)OC_1-C_4$ alkyl,15 (D) $C(O)$ heteroaryl,(D) $N(R^8)_2$,(D) $NR^8C(O)C_1-C_4$ alkyl,(D) $NR^8SO_2(C_1-C_4)$ alkyl,(D) OC_1-C_4 alkyl,20 (D) $OC(O)C_1-C_4$ alkyl,

(D)heterocyclic,

(D) SC_1-C_4 alkyl, or(D) $SO_2N(R^8)_2$;wherein C_1-C_8 alkyl, C_1-C_8 alkoxy, C_3-C_7 cycloalkyl, phenyl, aryl, heterocyclic,

25 and heteroaryl are optionally substituted with one to five substituents

independently selected from R^8 ; and provided that when R is halo or hydroxy it is not substituted on a carbon adjacent to a heteroatom;

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each R⁸ is independently:

- hydrogen,
oxo,
C₁-C₈ alkyl,
5 (D)C₃-C₇ cycloalkyl,
phenyl,
aryl or
heteroaryl,
wherein C₁-C₈ alkyl, C₃-C₇ cycloalkyl, phenyl, aryl and heteroaryl are optionally
10 substituted with one to three substituents selected from the group consisting of
C₁-C₈ alkyl, halo, and hydroxy; provided that the halo and hydroxy groups are
not substituted on a carbon adjacent to a heteroatom;

R⁹ is independently:

- 15 hydrogen,
(C₁-C₈) alkyl,
C₂-C₈ alkenyl,
C(O)C₁-C₈ alkyl,
C₂-C₈ alkynyl,
20 phenyl,
aryl, or
heteroaryl;

R¹¹ is independently:

- 25 hydrogen, (C₁-C₈) alkyl, or (D)phenyl, aryl;

D is: a bond or C₁-C₄ alkyl;

g is: 0, 1, or 2;

y is: 1 or 2;

- 30 m is: 1-4;

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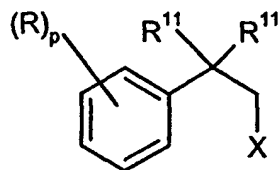
n is: 0-8;

p is: 0-4; and

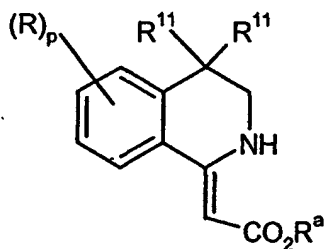
q is: 0-1;

5 comprising the steps of:

f) reacting a compound formula 1:

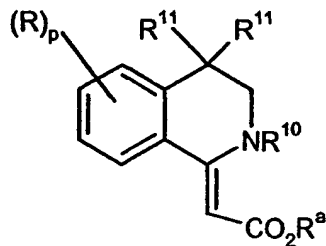


1;

wherein X is halo and R¹¹ is independently, hydrogen or C1-C4 alkyl, with CNCH₂CO₂R^a10 wherein R^a is C₁-C₈ alkyl, or benzyl to afford a compound of formula 2:

2;

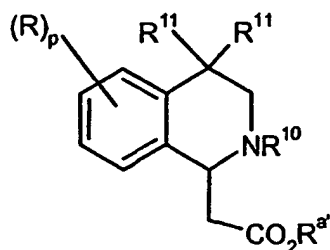
15 g) protecting the compound of formula 2 to form the compound of formula 3:



3;

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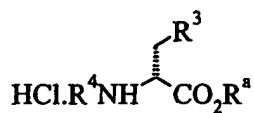
h) hydrogenating the compound of formula 3 to afford a compound of formula 4:



5

4;

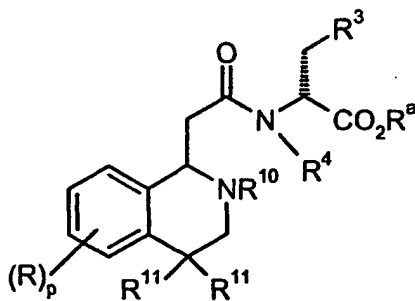
i) coupling the compound of formula 4 wherein R'a is hydrogen with a compound of formula 5:



10

5;

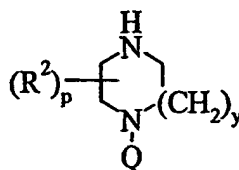
to afford a compound of formula 6:



6;

15

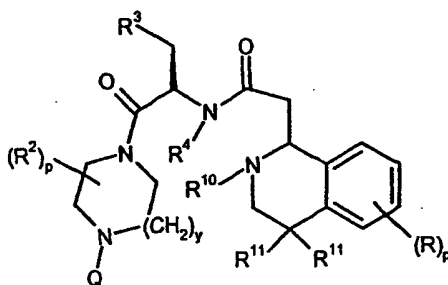
j) coupling the compound of formula 6 with a compound of formula 7:



7;

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to afford a compound of formula I:



I.

5 44. A method of preventing or treating obesity in a mammal comprising the administration of a therapeutically effective amount of the compound of formula I as recited in Claim 1.

 45. A method of preventing or treating diabetes mellitus in a mammal comprising the administration of a therapeutically effective amount of the compound of formula I as
10 recited in Claim 1.

 46. A method of preventing or treating male or female sexual dysfunction in a mammal comprising the administration of a therapeutically effective amount of the compound of formula I as recited in Claim 1.

 47. The method of 46, wherein the male or female sexual dysfunction is erectile
15 dysfunction.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/00033

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/496 C07D209/44 C07D217/16 C07D401/12 C07D409/12
C07D405/12 A61P3/04 A61P3/10 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 02 059108 A (MANCOSO VINCENT ; BIGGERS CHRISTOPHER KELLY (US); FISHER MATTHEW JO) 1 August 2002 (2002-08-01) claims	1-47
P, Y	WO 02 070511 A (RUEDIGER EDWARD H ; RUEL REJEAN (CA); THIBAUT CARL (CA); POINDEXTE) 12 September 2002 (2002-09-12) claims table 8 examples 300, 301, 310, 311	1-47
Y	WO 00 74679 A (PATCHETT ARTHUR A ; PLOEG LEONARDUS H T V D (US); SEBHAT IYASSU (US) 14 December 2000 (2000-12-14) claims	1-47
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *g* document member of the same patent family

Date of the actual completion of the international search

9 Apr11 2003

Date of mailing of the international search report

17/04/2003

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Authorized officer

Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/00033

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 64002 A (PATCHETT ARTHUR A ;PLOEG LEONARDUS H T V D (US); YE ZHIXIONG (US);) 16 December 1999 (1999-12-16) cited in the application claims	1-47
A	WO 01 70337 A (MERCK & CO INC ;NARGUND RAVI P (US); PALUCKI BRENDA L (US)) 27 September 2001 (2001-09-27) claims	1-47

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/00033

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 44-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int lonal Application No

PCT/US 03/00033

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02059108	A	01-08-2002	WO 02059117 A1 WO 02059108 A1	01-08-2002 01-08-2002
WO 02070511	A	12-09-2002	WO 02070511 A1 WO 02079146 A2 WO 02069905 A2	12-09-2002 10-10-2002 12-09-2002
WO 0074679	A	14-12-2000	AU 5306800 A EP 1187614 A1 JP 2003505435 T WO 0074679 A1 US 6350760 B1 US 2002137664 A1	28-12-2000 20-03-2002 12-02-2003 14-12-2000 26-02-2002 26-09-2002
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WO 0170337	A	27-09-2001	AU 4928101 A EP 1268000 A1 WO 0170337 A1 US 6472398 B1	03-10-2001 02-01-2003 27-09-2001 29-10-2002